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RESEARCH ARTICLE

Evaluation of Anti-Ulcer Activity of Avipattikar Churna in Ethanol Induced Ulcers in Rats

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ABSTRACT

Avipattikar churna, a polyherbal formulation, is one of the popular ayurvedic formulations which is used for peptic ulcer disease. The present study was carried out to evaluate anti-ulcer activity of avipattikar churna in experimental induced ulcers in rats by ethanol induced model. Avipattikar churna was evaluated for gastroprotective activity at a dose of 500 mg/kg (p.o) and 750 mg/kg (p.o) respectively. Depending on the model, outcome measures was body weight, ulcer score, volume of gastric juice, pH of gastric juice and Gastric acidity. Data was analyzed using one-way analysis of variance and $p<0.05$ was considered as statistically significant. The churna, in both doses, significantly inhibited bodyweight, ulcer score, volume of gastric juice, pH of gastric juice and Gastric acidity in ethanol induced model as compared to positive control group. This may be due to enhancement of the gastric mucosal defensive factors in ethanol induced ulcer model. The effects of the churna were comparable to that of ranitidine. It was concluded that Avipattikar churna shows anti-ulcer effect by healing peptic ulcer and also prevent the development of peptic ulcer disease in rats.

Keywords: Avipattikar churna, peptic ulcer, gastric acid, gastroprotective activity, Ranitidine, Ethanol, Rats.

INTRODUCTION

Peptic ulcer is one of the common gastro-intestinal diseases, in the lower esophagus, stomach or the intestinal mucosa. The ulceration results due to imbalance between aggressive and defensive factors of the gastro-intestinal mucosa. Peptic ulcer largely affects adult males. Women seems to be peculiarly immune to peptic ulceration during the child bearing age. Gastric ulcers occur frequently in the old age group and in lower socio-economic class of individuals. Duodenal ulcers occur commonly in younger individuals [1]. Peptic ulcer disease is associated with upper abdominal pain, bloating, weight loss, heartburn, lack of appetite and nausea which can be treated with various drugs like proton pump inhibitors, H_2 receptor antagonist which have fast therapeutic action and proves

efficacious [2]. Due to drawback of Allopathic medicine people are interested in herbal formulations [3]. Avipattikar churna is an ayurvedic polyherbal formulation **"**avipatti**"** means "to get rid of digestive disorder", which is comprised of 14 different ingredients are Sonth(*Zingiber officinale*), Black pepper(*Piper nigrum*), Long pepper (*Piper longum*), Haritati *(Terminalia chebula)*, Bibhitaki (*Terminalia bellirica*), Amla(*Embilica officinalis*), Mustaka(*Cyperus rotundus)*, Vaividang(*Embelia ribes*), Green cardamom(*Elettaria cardamomum*), Tejpatta(*Cinnamomum tamala*), Laung (*Syzygium aromaticum*), Nishoth (*Operculina turpethum*), Misri(Candy sugar) and Salt(*Vida lavana*) [4].Avipattikar churna possesses strong carminative, antioxidant and anti-inflammatory properties which helps in curing imbalances related to pitta dosha and in turn promote healing from hyperacidity, gastritis, indigestion, anorexia, urinary retention, constipation and piles. Avipattikar Churna is an ayurvedic medicine used in clinical practice in dealing with the case of gastric disorders since the 19th century. According to ayurvedic physicians, ulcer is formed as a result of improper digestion of food. Avipattikar churna gives a relief from sour and bitter eruption, inflammation in throat, chest and abdomen and sour salivation. It also removes heat from the intestine, providing an antidote for pungent food.

Avipattikar churna is used to treat hyperacidity share a good portion of the drug market. Due to its higher safety and efficacy, it may be a good substitute for acid-lowering drugs of today. The main ingredient of avipattikar churna is nishotha.It has katu, rasa, laghu, ruksha, tikshna guna, ushna virya and katu vipaka. It also contains triphala which is mild purgative. The second ingredient is clove.Candy sugar is added to mask the pungent and bitter taste of other content used in the formulation.Ingredients such as Haritaki, Maricha & Pippali exerts cytoprotective effects on the gastric mucosa [5,6,7], Sonth decreases the gastric secretion, increase mucosal resistance and potentiates the defensive factors of mucosa [8]. Laung helps in maintaining the basal gastric mucosal blood flow and increases the mucus secretion [9]. Therapeutic dose of churna for peptic ulcer disease is 3-6g with water before or after meals. Hence, the current study reports the anti-ulcer activity of aqueous extract of avipattikar churna on ethanol induced peptic ulcers in rats by comparison with reference to the standard drug ranitidine [4].

MATERIALS AND METHODS

Collection and Preparation of marketed product of Avipattikar churna

The Avipattikar churna was procured from Baidyanath Amazon mart. Avipattikar churna 10 mg was dissolved in 10ml distilled water. The dose of the drug was calculated based on the body weight of the animals. The drug was administered through oral route.

Animals

A total of 30 male wistar rats weighing 200-250 gms was obtained from the animal facility and used for the study. The rats were maintained under standard environmental conditions and was fed with standard pellet diet and water *ad libitum*[10]. The experiments were performed as per the guidelines of Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA). The animals were grouped into five groups. Each group contains six animals.

Grouping of animals as follows: -

Group 1: Negative control

Group 2: Positive control (Ulcer was induced)

Group 3: Animals treated with Low Dose Avipattikar churna (LDAC) (500 mg/kg b.w, p.o.)

Group 4: Animals treated with High Dose Avipattikar churna (HDAC) (750 mg/kg b.w, p.o.)

Group 5: Animals treated with Standard dug Ranitidine (150 mg/kg b.w, p.o.)

METHODOLOGY

Ethanol Induced Method

The healthy wistar rats were taken for the study and were divided into five groups. Group 1 and Group 2 received normal diet, Group 3 received LDAC (500 mg/kg b.w, p.o.) and Group 4 received HDAC (750 mg/kg b.w, p.o.) and Group 5 received Ranitidine (150 mg/kg b.w, p.o.) for 7 days. The animals were fastened for 12 hrs prior to the ulcer induction with water *ad libitum*.On the 8th day ulcer was induced by administration of ethanol at a dose of 1 ml/gm of body weight, orally, after 45 minutes of oral administration of LDAC, HDAC and Standard (Ranitidine 150 mg/kg b.w, p.o.) to respective groups of animals including Group 2 which was untreated. Animals were sacrificed one hour after ethanol administration.The stomach was removed, cut along the grater curvature, gastric juice was collected, after that washed with normal saline (0.9% NaCl)[11].

Determination of anti-ulcer activity parameters [12]

Ulcer index: -

The dissected stomachs of the sacrificed rats were opened along the greater curvature and the ulcer index was calculated from the glandular portions of the stomach.

The ulcer index was calculated as,

Ulcer index= 10/x

Where x=Total mucosal surface/Total ulcerated surface.

Score the ulcers as below

0= Normal colored stomach

0.5= Red coloration

1= Spot ulcer

1.5= Hemorrhagic streaks

2= Ulcers > 3 but <5

3= Ulcers > 5

Volume and pH of gastric secretions

In a graduated test tube, the contents of the dissected stomachs were taken and are allowed to centrifuge at 200 rpm for 10 min. The supernatant liquid was measured for the volume of gastric juice and expressed as ml/4hrs and pH of the gastric juice was measured.

Gastric acidity [13,14,15]

In the conical flask, the supernatant liquid of the gastric juice was taken, and two drops of topfer's reagent was added. In a burette 0.01N, NaOH was added and allowed to triturate till the flask changed to yellow Colour. Then two drops of phenolphthalein were added and triturate till orange colour was reached.

Acidity was calculated by using the formula:

Acidity= (volume of NaOH ×Normality of NaOH ×100)/0.1mEq/L

STATISTICAL ANALYSIS:

The statistical significance was assessed using one-way analysis of variance (ANOVA). For comparing nonparametric body weight, ulcer scores, volume of gastric juice, pH of gastric juice and Gastric acidity, ANOVA test was used. The values are expressed as mean ± SEM and $p < 0.05$ was considered significant

RESULTS AND DISCUSSION

Evaluation of Ant-ulcer activity of Avipattikar churna in ethanol induced ulcers in rats (Fig.1). Both the doses of Avipattikar churna showed a significant reduction in body weight compared to positive control. High dose Avipattikar churna (HDAC) showed more reduction in body weight than Ranitidine (Standard) in ethanol induced ulcer model. Values are expressed in terms of Mean±SEM statistical analysis was carried by GraphPad Prism 9 through one way ANOVA, $P < 0.05$; was considered as a significant (Fig.2.). Both the doses of Avipattikar churna showed a significant reduction in ulcer score compared to positive control. High dose Avipattikar churna (HDAC) showed more reduction in ulcer score than Ranitidine (Standard) in ethanol induced ulcer model. Values are expressed in terms of Mean±SEM statistical analysis was carried by GraphPad Prism 9 through one way ANOVA, $P < 0.05$; was considered as a significant. (Fig.3).

High dose of Avipattikar churna (HDAC) showed more reduction in volume of gastric juice compared to positive control and Ranitidine (Standard) in ethanol induced ulcer model.Values are expressed in terms of Mean±SEM statistical analysis was carried by GraphPad Prism 9 through one way ANOVA, $P < 0.05$;was considered as a significant (Fig.4). Both the doses of Avipattikar churna showed a significant reduction in pH of gastric juice compared to positive control. Values are expressed in terms of Mean±SEM statistical analysis was carried by GraphPad Prism 9 through one way ANOVA, $P< 0.05$;was considered as a significant (Fig.5). Both the doses of Avipattikar churna showed a significant reduction in Gastric acidity compared to positive control. High dose Avipattikar churna (HDAC) showed more reduction in Gastric acidity than Ranitidine (Standard) in ethanolinduced ulcer model (Fig.6).

Values are expressed in terms of Mean±SEM statistical analysis was carried by GraphPad Prism 9 through one way ANOVA, $P < 0.05$;was considered as a significant. In most cases the stable incidents of ulcer in rat model provide a powerful and convenient method for the investigation of therapeutic model for the disease and for its complications Peptic ulcers are due to an imbalance between offensive (NSAIDs, alcohol, acid, pepsin) and defensive (bicarbonate, mucosal blood supply, prostaglandins) factors. Acid and pepsin are relatively less important causative agents, but defects in the defensive mechanism of gastric mucus are the first step toward ulcer formation [16].

The aim of this study was to evaluate the anti-ulcer activity of avipattikar churna by ethanol induced model in rats. The avipattikar churna showed dose dependent, ulcer protective effects against ethanol induced model. The necrotizing agent ethanol is a widely used ulcer inducing agent in ethanol induced model, because it easily and rapidly penetrates into the gastric mucosa[17,18]. Ethanol induce gastric damage is through the leukotriene production and 5 lipo-oxygenase pathways. Prostaglandins will play a major role in ethanol induced ulcers So it shows that the drugs which are effectivity against ethanol induced ulcers can possess gastric mucosal membrane protective actions. The cytoprotective action stimulates the prostaglandin synthesis which intern protects the gastric mucosa.

Ethanol induced lesion formation is multifactorial. The factors involved in the formation of ulcers using ethanol are described by Lange et al., 1985, koo et al., 1986 suggested that the gastric wall mucous depletion induced by ethanol is one of the pathogenic mechanism responsible for the gastric lesions. The number of lesions present in the gastric mucosa for the indicative of the severity of the ulcer disease. The diameters of the lesions are used for the determination of the ulcer index a measure of the ulcers in the gastric mucosa. The ethanol induced ulcer which are predominant in the glandular portion of the stomach are reported to stimulate the formation of leukotriene C4 resulting in the damage of rat gastric mucosa. The observed decrease in the ulcer index of avipattikar churna may be due to anti-secretory or cytoprotective property of it. In this study, ulcers are induced by administration of ethanol showed comparatively more extensive mucosal lesions and edema because of neutrophil infiltration in the ulcerated gastric tissue. LDAC and HDAC treated animals showed protective effects against ethanol induced ulcer by reducing ulcer score, volume of gastric juice, pH of gastric juice and gastric acidity compared to positive control

group which Indicates the gastro protective effective of avipattikarchurna Ranitidine did not overcome the mucosal depletion induced by ethanol since it acts via by blocking H2 receptor [19,20]. On contrary mucosal depletion by ethanol was overcome by avipattikarchurna which underlies its cytoprotective activity. Statistical analysis was carried by GraphPad Prism 9 through one way ANOVA, $P<0.05$; was considered as significant. The High dose Avipattikar churna (HDAC) significantly ($p<0.05$) inhibited body weight, ulcer score, volume of the gastric contents, pH of gastric juice and gastric acidity in ethanol induced model as comapared to positive control group. This may be due to enhancement of the gastric mucosal defensive factors in ethanol induced ulcer model. The effects of the churna were comparable to that of ranitidine

CONCLUSION

The results of the present study demonstrated that avipattikar churna (500mg/Kg, 750mg/Kg) protected gastric mucosa and has ulcer-protective activity. As it is evident by the significant inhibition of ulcer model avipattikar churna (500mg/Kg, 750mg/Kg) produces a significant, dose dependent gastro protective effect in ethanol. It is concluded that an avipattikarchurna as a poly-herbal Ayurvedic formulation possess significant gastro protective effects.

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Table: 1. Mean and SEM of body weight, ulcer index, volume of gastric juice, pH of gastric juice and Gastric acidity for ethanol-induced ulcers.

Treatment	Dose Mg/kg	Body weight	Ulcer index	Volume of Gastric juice	pH of gastric juice	Gastric acidity
Negative Control	0mg/kg	213.16±1.42	0	6.65±0.177	7.81±0.1977	0.64±0.0122
Positive Control	Ethanol (1ml/g)	221.66±1.914	3.5±0.311	5.5±0.066	4.65±0.1257	1.068±0.1728
Low dose Avipattika Churna (LDAC)	500mg/kg	215±1.665	1.33±0.2714	7.4±0.0644	5.25±0.0991	0.525±0.003204
High dose Avipattikar Churna (HDAC)	750mg/kg	213.66±1.4244	0.5±0.144	5.18±0.1036	4.2±0.1024	0.358±0.0072
Standard (Ranitidine)	150mg/kg	216.66±2.253	1.33±0.1922	6.18±0.1187	5.416±0.0862	0.753±0.00804

Fig.1. Evaluation of Ant-ulcer activity of Avipattikar churna in ethanol induced ulcers in rats

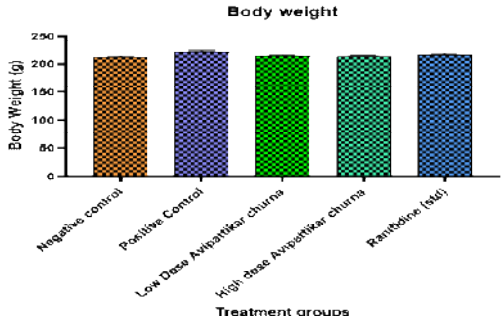

Fig. 2: - Effect of Avipattikar churna and Ranitidine (Standard) on body weight in Ethanol induced ulcers in rats

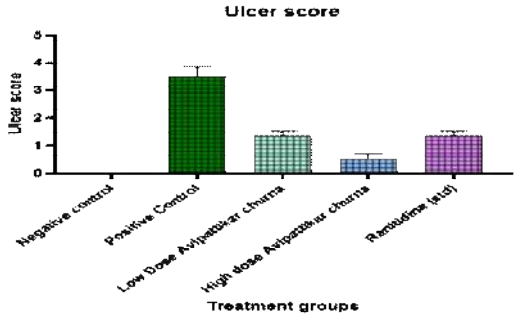

Fig 3: - Effect of Avipattikar churna and Ranitidine (Standard) on ulcer score in Ethanol induced ulcers in rats

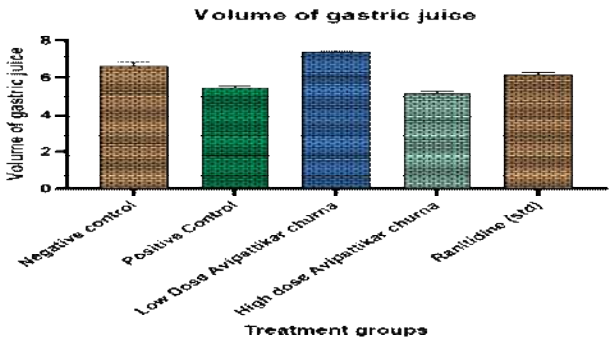

Fig 4:- Effect of Avipattikar churna and Ranitidine (Standard) on volume of gastric juice in Ethanol induced ulcers in rats

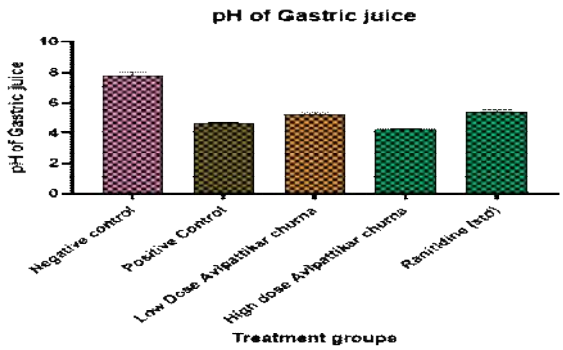

Fig 5:- Effect of Avipattikar churna and Ranitidine (Standard) on pH of gastric juice in Ethanol induced ulcers in rats

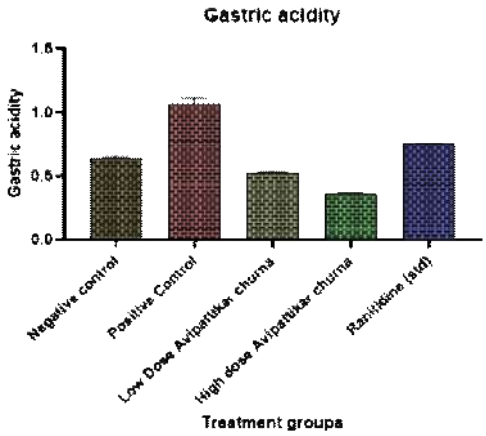

Fig 6:- Effect of Avipattikar churna and Ranitidine (Standard) on Gastric acidity in Ethanol induced ulcers in rats

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RESEARCH ARTICLE

Zonation of Landslide Susceptibility in Saitual Town Area, Mizoram

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ABSTRACT

A landslide occurs when soil, rock, or organic material slides down a slope due to gravity's impact. Landslide be caused by various factors, including heavy or continuous rain, earthquakes, slope fluctuations, geomorphology and anthropogenic activity. Mizoram is one of India's most vulnerable landslide regions. During the monsoon season, the state of Mizoram is prone to landslides. Though landslides occur naturally, human meddling is one of the key reasons contributing to landslides in cities and townships. Since, geology of Mizoram is very young, landslides can impact economic loss of the state. The state's various landforms comprise ridges that have been dissected by deep canyons, spurs, keels, and other features. Steep fault scarps have formed from faulting. As a result of its hilly terrain, Mizoram is vulnerable to landslide hazard. Human actions and geological processes, which are enabled by environmental factors, create the majority of the damage, which varies widely from place to place. Saitual town is situated in north eastern part of Aizawl district. Geo-spatial technology has advanced recently and geographic information system technique have enabled to understand landslide processes in more depth. Geo-spatial data were used in this study to map the several landslide susceptibility in Saitual town in order to implement mitigation measures and identify likely occurrence zones. Landslide suscepbility zones are mapped and generated using satellite data. Slope stability is the subject of an in-depth investigation and was also carried within the study area. The study area falls under Tertiary sediments which are mostly composed of Arenaceous and Argillaceous sandstones and shale inter bedded of Bhuban formation. The main purpose are to analyze landslide vulnerability and mapping, identify landslide hazard zones, and suggest mitigation measures using approaches that include extensive fieldwork and data collection, data analysis and the creation of thematic layers.

Keywords: Landslide susceptibilit, Remote sensing and GIS

INTRODUCTION

The term landslide refers to the downward sliding movement of huge quantities of land masses and earth particles. The sliding movement of the rock masses occurs from a higher level to a lower level, mostly in steep sloping areas. Landslides, which are a type of mass wasting, are the most devastating event that occurs when soil and rocks flow down slope due to gravity. Landslide can be occurred due to a number of factors including heavy or continous rainfall, geomorphology, anthropogenic actions and slope variations. Toppling, debris flow and slides are all examples of landslides. Landslide susceptibility's concept entails estimating the zones of landslide-prone areas depending on the spatial distribution of factors related to instability processes without regard to time. It can also be used to express relative risk, total landslide density, and predicted landslide density. It covers the grading and geographical distribution of terrain units based on their landslide vulnerability. This is influenced by geology, climate, topography, anthropogenic and vegetation influences including development and vegetation clearing. Mizoram is among the most landslide prone state in India. Mizoram is known for its high slopes and relief. The area's slope is frequently 45 degrees or more. The loose and unconsolidated sediments that make up these high slopes and reliefs are common. It also increase` the potential risk of landslide occurring.

Rainfall is one of the main causes of landslides in Mizoram, as seen by the dramatic spike in landslide occurrences during the monsoon season. In India, the north-east region is under the influence of the south-east monsoon, Mizoram experiences an abundance of rain throughout this season. Rainwater causes landslides by increasing soil and rock pore water pressure, lowering resistance of shearing and triggered landslides. Anthropogenic activities like road cutting, agricultural and urbanization also influenced landslides (Chandel et al. 2011). Every year during the monsoon season, the state is devastated by landslides. The magnitude of the damage produced due to this kind of danger varies greatly from one place to another and is mostly caused by anthropogenic activities, as well as geological and environmental. It was comprised of alternating strata of sandstone-shale, crumpled-shale and shale-siltstone from the Surma Group's Middle Bhuban Formation. The Surma Group of rocks is found unconformably on top of the Barail Group, whereas the Tipam Group is found conformably beneath it. The Bhuban and BokaBil Formations belong form the Surma Group of rocks (Ganju 1975). These sedimentary successions are from the Tertiary Period with a thickness of around 8000m are characterized by a arenaceous and argillaceous alternation composed of sandstone, silty-sandstone, siltstone and shale.

To demarcate landslide hazard zone thorough landslide susceptibility mapping was carried out for Saitual town. Based on a number of factors such as geological structure, slope and landuse/land cover, a landslide susceptibility zone was created. Saitual was divided into five : very high zone, high zone, moderate zone, low zone and very low zone. Our study, which would not have been possible without geo-spatial technology, has recognised the value of these techniques. The aim of landslide susceptibility zonation is to divide the study area into zones with comparable susceptibility to the mass movements occurring. There are two types of methods: direct method and indirect method. One of the direct techniques is geomorphological mapping in which landslides have occurred in the past and are now occurring and assumptions about the causes of instability are developed, followed by zonation of those places most inclined to disaster. The degree of susceptibility is mapped through a direct mapping approach in the field before recognized as a result of the fieldwork with toposheet. This process is known as the qualitative method. The indirect method consists of two methodologies: heuristic and statistical (data-driven). Other factors include rock type, slope, land use and landform. That influence landslides are graded and In the heuristic method, the factors are weighted based on their presumption or potential influence in causing debris flow or mass movements.

METHODOLOGY

Study area

The town of Saitual is situated in Mizoram's north-eastern region in north-east India. The area of the town is 12.34 sq. km and situated between the longitudes of 92° 56' 30" and 93° 59'11" east and the latitudes of 23° 38'23" and 23°

44′ 45" north. It's on toposheet No. 84A/14 from the Survey of India. The figure1 represent the study area. The average annual rainfall of the study area is 1506.9 mm, the entire Aizawl district is directly influenced by the south west monsoon (IMD 2019).

Data

The main data were stereo-paired Cartosat-I data from the Indian Remote Sensing Satellite (IRS-P5) with a spatial resolution of 2.5 m and Quick bird data with a spatial resolution of 0.8 m from the Indian Remote Sensing Satellite (IRS-P5) (IRS-P5). Additional references to SOI topographical maps, as well as numerous supplementary data, were made.

Themes

Using ArcGIS software and field data in the GIS domain, several with the provided data and the SOI map, thematic layers related to the primary factors accountable to the prevalence of landslides were developed in this area.

Slope

Mizoram is known for its hilly terrain and high relief. The slope of the state is typically 45 degrees or more. The loose and unconsolidated sediments that make up these high slopes and reliefs are common. This also raises the chances of a natural calamity occurring. The slope was created using the Indian Remote Sensing Satellite (IRS-P5) stereo paired. The Digital Elevation Model and Cartosat-I data (DEM). Slope is the main factor to consider when considering stability since it has a significant impact on the susceptibility of infrastructure and urban design. The slopes in the study area are measured in degrees and divided into five slope aspect, namely 20–25, 25–30, 35–40, 40–45, and over 60 degrees. Shear stress can be found in soil or other unconsolidated materials increases as the angle of the slope increases and creating a zone of increased landslide potential. Further to that, values are assigned based on the slope gradient. After determining the slope gradient, values are given. Slope statistic is show in table 1 and fig. 2 shows slope map.

Geological Structure

Geological structure of the study area such as fractures, faults, joints and lineaments can be monitored. Data from remote sensing is used to calculate it. (Kanungo et al., 1995). Several faults and fractures of varying magnitudes and lengths pass through the study area's exposed rocks, which are mainly the important factors for landslide susceptibility (Saha et al., 2002). MIRSAC (MIRSAC, 2006). Near fault zones and geological formations, landslides are more likely to cause problems. For analysis, 50 m buffer zones were created on all lineaments, including faults, on both sides. The geological structure is represented by a geological map. The studied area is located within the Bhuban formation of the Surma Group of Tertiary age (GSI, 2011), which is classified into Lower, Middle and Upper formations. Within the study area, Middle Bhuban, which is mostly argillaceous rock, is exposed. The study region has been classified into different litho-units based only on types of the exposed rock. The four types are crumpled shale, sandstone-shale and shale-sandstone and shale-siltstone. Landslides are mostly occur in shale and siltstone lithological units than in hard compact sandstone-shale complexes. The most prone to landslides among the rock types in the area is Crumples shale is. Weightage values are assigned for analysis in accordance with this. Figure 3 shows geological map and lithological statistic in shown table 2

Land use and Land cover

As it influences the rate of erosion and weathering, land use / land cover is one of the main factors in influencing landslide susceptibility. It is categories as Dense vegetation, moderate vegetation, scrubland, built-up and barren land. Landslides were thought to be less likely to occur in areas with thick vegetation cover. (Mohammad Onargh *et al.,* 2012). As a result, the class of Dense Vegetation was assigned to low weightage. Since built-up areas were found to be more prone to landslides as compare to other classes (Pandey et al., 2008) and assigned to a higher weightage. The statistics of land use and land cover is show in table 3 and fig. 4 shows land use/ land cover map.

Data Analysis

The initial step was to conduct a landside inventory along the road and settlement area, where active and dormant landslides were located, analyzed in a GIS system. Environmental factors such as slope morphometry, lithology, geomorphology, land use / land cover and geological structure were found to have a significant impact on the incidence of landslides in the study area. These six themes are divided into appropriate classes and act as the important parameter for landslide susceptibility and classes in each parameter were studied to determine their related to landslides. Each class is assigned a weightage value based on its landslide risk, with lower weightage indicating the least influence on landslide incidence and higher weightage indicating the most influence on landslide. The importance of the various categories within a parameter is decided by the experts prior experience in determining their anticipated or expected importance in causing a landslide. Also ground data on the occurrences of landslides in the study area was taken into consideration. To calculate landslide susceptibility, combined of thematic layers and analyzed in a geo-spatial environment. Joyce and Evans devised a weightage mechanism and a stability rating system based on the National Remote Sensing Agency (NRSA 2001).

RESULTS AND DISCUSSION

Combination of the influencing parameters assigned by various weightage values to each thematic layers. The susceptibility map was prepared and divided into four zones i,e very high, high, moderate, low and very low zones. The Saitual town map is prepared using a scale of 1:5,000.The susceptibility map is show in Fig 5.

Very High Susceptibility Zone

It covers the areas of high risk mass movement and debris flow due to erosion steep slopes being covered in weathered rock and soil debris when disturbed. This is geologically unstable and slope collapse may occur, after extensive torrential rain. Furthermore, the zone with areas where the rock incline and the area slope both are very highly steep and the direction is the same. Within this zone, during and after a prolonged heavy rainfall, severe instability may happen. In the high susceptibility zone, a number of fault lines, joints, and fractured zones run transversely as well. These include areas that are susceptible to long-term water erosion due to the lithology of soft permeable nature, an unconsolidated underlying load, and a lack of proper drainage.

High Susceptibility Zone

It includes landslide-prone area with steep slopes when disturbed. It include areas where weathered rock and soil debris pose a significant risk of sliding debris. Furthermore, this area consists areas where the rocks dipping and the area's slope, which is usually fairly steep (approximately 45 degrees or more), are in the same direction. The high susceptibility is also traversed by several lineaments, fractured zones, and fault planes. Streams erode these areas on a regular basis. It is frequently observed in the vicinity of the Very High Susceptibility. It is geologically unstable as a result. Allocation of housing structures and other buildings should be limited within this zone, and cautions and preventive measures should be readily available if they are absolutely necessary. It is also recommended that suitable stream canalization and drainage system development be carried out where erosion may occur along streams.

Moderate Susceptibility Zone

It is considered stable and it includes areas with moderate vegetation, a moderate slope gradient. The rocks are moderately compacted hard as well as the least amount of RCC construction in this zone. Although areas with steep slopes may be included in this zone (more than 45 degrees), they are less susceptible due to the direction in which the rock bed is inclined and the lack of overlaying debris and anthropogenic activities . The zone of moderate susceptibility is widely dispersed throughout the area and constitutes most f the study area. This zone also provides a broad portion of the human settlement. Since, it is typically regarded stable, some part of this areas may possibly unstable. It is important to identify such areas using detail maps and appropriate mitigation measures must be

adopted. Seismic activity and continual severe rainfall, on the other hand, may risk stability of this zone. As a result, Drainage systems must be well-planned and maintained and slope modifications should be minimized to the greatest extent practicable. This zone should not be used for any activity carried out by humans that could induce landslides and slope failures. Regardless of the fact that this zone comprises locations that are currently stable. It will be determined by future land-use activity. Therefore, human activities must be investigated and planned effectively to sustain its current status.

Low Susceptibility Zone

It include areas, there are the interaction of influencing parameters has a lower probability to have a significant impact on slope stability. In this zone, the slope failure possibility is low or non-existent given the current environmental conditions. Though certain areas may have minimal vegetation, the vegetation is often dense. Because the slope angle is modest mostly less 30 degrees. Soft and unconsolidated sediments cover several of the areas and the landslide potential is low. This zone has areas with gentle slopes and flatlands. This zone is confined mainly to places with little or no anthropogenic activity and is widely spread throughout the study area. Unless large site alterations occur that render this zone ideal for implementing development initiatives. Within this zone, any type of development activity, as well as the distribution of It is possible to construct residential constructions in a safe condition. The rocks have a low amount of dip and slope angles. In some areas, despite the presence of soft rocks and underlying soil debris, the possibility of slope failure is reduced due to the low slope angle and the presence of vegetation.

Very Low Susceptibility Zone

Low slope angles and dense vegetation characterize this zone. As a result, it is assumed that it is landslide-free now and in the future. The rocks dip and slope angles are extremely low. The low slope angle indicates the probability of slope failure, despite the presence of soft rocks and underlying soil debris in several areas.

CONCLUSION

Human activities with combination of natural factors such as slope, geological structure, lithology, and relative relief as well as Infrastructure and road construction have transformed several areas of Saitual town very high susceptible to landslides. In this case, it critical for extensive preventive plans in place for future development efforts, as well as to raise public awareness. With high-resolution satellite image, satellite remote sensing and GIS as well as thorough verification on the ground and fieldwork have shown that effective tools for landslide susceptibility zonation. The landslide susceptibility zonation generated by this study will be valuable for adopting measures to mitigate as well as planning future development and expansion of Saitual town. It will be useful for studying and mapping landslide-prone zones, assessing prospective development areas, and creating a database for landslide risk studies in the area.

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Table 1: Slope Statistics

Slope Degree	Area in sq.km	Percentage (%)
20-25	9.57	78.17
25-30	1.17	9.509
30-35	0.76	6.195
35-40	0.48	3.895
40-45	0.33	2.693
>60	0.02	0.174
Total	12.34	100.00

Table 2: Lithological statistics

Rock Type	Area in sq.km	Percentage
shale_ siltst	6.39	51.79
shale_ sst	3.93	31.87
Sst_ shale	1.93	15.66
Crumpled_ shale	0.08	0.68
Total	12.34	100.00

Table 3: Land use and Land cover statistics

Land use and Land cover	Area in sq.km	Percentage (%)
Dense vegetation	4.76	38.57
Moderate vegetation	3.62	29.32
Scrubland	2.82	22.83
Build up	1.06	8.58
Barrenland	0.09	0.70
Total	12.34	100.00

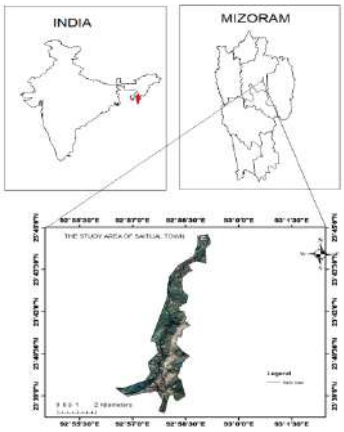

Figure 1: The study area of Saitual town

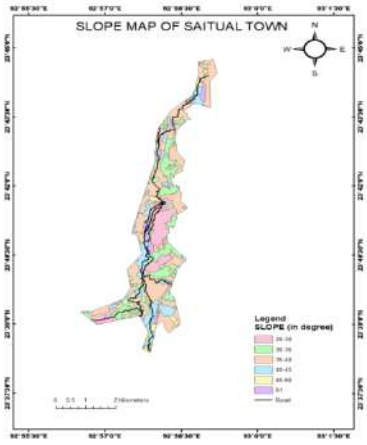

Figure 2: Slope map

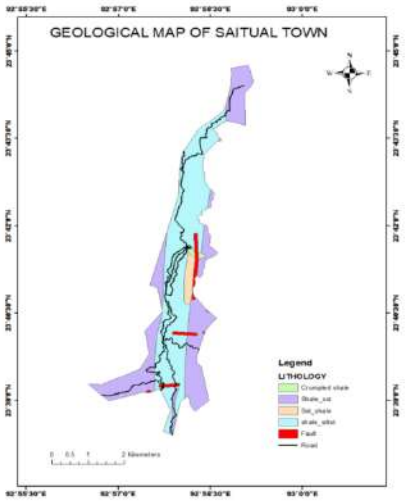

Figure 3: Geological map

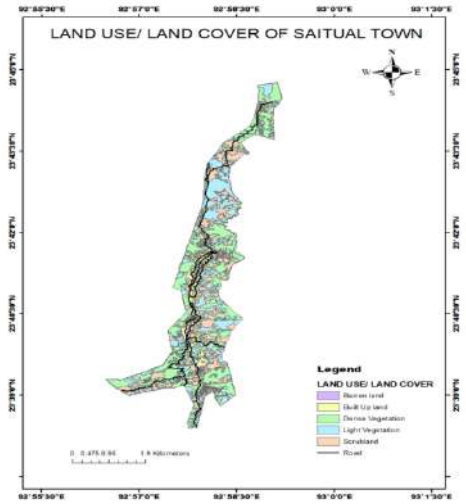

Figure 4: Land use and land cover map

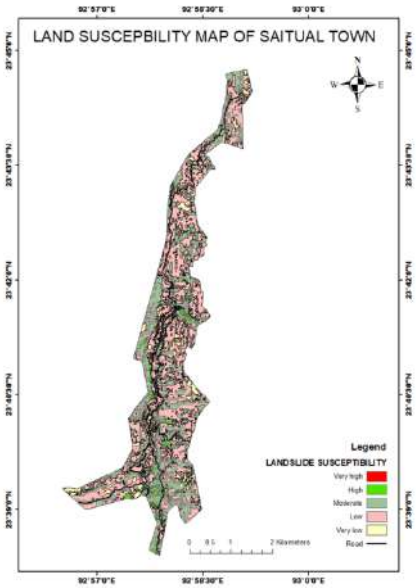

Figure 5: Landslide Susceptibility map of Saitual town

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RESEARCH ARTICLE

Choices, Chances, Changes- The Perpetual Quandary of Discretion and Virtues

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ABSTRACT

History is too convoluted to teach uncomplicated lessons. It not only serves as the foundation of a nation, empire or a civilization but also provides factual records of the intricate choices or decisions taken by the authorities time to time. This is a different but important reason to read history for. Though clear parallels are rare between the past and present situations but it provides a deeper understandings of the complexities of the present problems. The major Indian epics like *the Ramayana* and *the Mahabharata* help in dismantling the facile lessons from the past and prepares the modern minds to face challenges of the present. Through the choices made by the major characters in these epics, the current decisions and policies made by government in pandemic time are evaluated in this study. Providing an analytical empathy for the history it focuses on the context and reflects the importance of our past epics. It presents the critical questions of ethical dilemmas which make the authority to stand in docks and make a difficult choice between personal principles or public good, between egocentrism or neglecting individual preferences.

Keywords: Mythology, History*, Mahabharata, Ramayana,* Ethical Dilemmas, Choices

INTRODUCTION

History is a cyclic poem written by time upon the memories of man. Percy Bysshe Shelley from being a part of fire ball to the development of planet earth, from its evolution to the present day, humans have read a lot about these facts in the history of civilization. Apart from providing us names, dates, events & concepts, most importantly history gives us understanding and meaning. In an era of standard-based accountability, the critical ability and

meaningful development of interpretations have become a vital part of everything, especially in a country full of diversities in name of religion, gods and culture. India has a prominent place for mythologies. These mythologies are not just taught to show the fancies or perspectives but also stories of humility, movements, intentions and most importantly hope. So history through these mythologies provide us narratives to think critically, move forward, identify the mistakes and lessoned from them so that ultimately a better existence can be created for all .

The Narrative of History and Present

Mahabharata and Ramayana being part of every house almira and the temple, are the mythologies which every child to old one remember. The prominent incidents of these mythologies are known even to those who have never read it. These classics are not confined just to the religion but also present a clear picture of ethical dilemmas, which are inseparable part of India till the present day.

What should be chosen, what should be given priority, what should be the dharma and how to choose what is right, are the questions interrogated from the ancient times till now. In this pandemic times when it has become risky to breath in open air, the question of choices is the for most. There have been certain questions from past till today which are ambiguous and need to be answered.

- What should be the ultimate good?
- Who should rule and decide?
- Whose government is for whom?
- What is more important individual or the society?

The critical questions of ethical dilemmas make the authority or the king in power to stand in docks and make a difficult choice between personal principles or public good, between egocentrism and neglecting individual preferences. If we look at the two important epics *Ramayana* and the *Mahabharata* their value is not limited to the religious or entertainment purpose, but they also present the difficult public policy choices faced by the authorities or the people in power. Considering them, many of the policies or choices were easy to make, many of them are still debatable. And as we generally state that history repeats itself, the same situation of choices we are facing today, during this pandemic time.

Objectives of the Study

-to understand the moral dilemma and status presented in Indian mythology
-to analyse the pandemic state
-to critically evaluate the past and present situations and providing required solutions

METHODOLOGY

This study consist of close reading, reinterpretation and in-depth study of epics- the *Mahabharata and the Ramayana* along with the present data of pandemic. This research paper also considers the critical material and reviews available on various sites and books.

The Tough Choices from the *Ramayana*

Ramayana full of ideals set for a good ruler, also provides us certain instances where a king being the epitome of sacrifices for his subjects, was forced to neglect what was good for the public and choose to keep his promises, so that the future posterity cannot question on his promises. It is a complex question to answer that was he right when he choose to honour his words of providing two boons to queen Kaikai who had rescued his life? Was not such a prudent king sucked in such confusion? Was not he had the vision that Rama, his eldest son, would have benefited the kingdom by his wisdom, instead of sending him into exile. Did king Dashrata made the right choice between doing appropriate to his subjects and also keeping his subjects and also keeping his individual integrity as a ruler or authority whose word could be always trusted? Rama being an obedient son, followed his father's order without giving any second thoughts, but again the moral confusion interrogates on Rama's decision as if it was right for him

to accept his father's wishes of going into exile, or should he had given priority to his subjects who required him to rule and refuse to the unreasonable demand of his step mother Kaikai.

The Vedas an Upanishads state the ideal king who gives priorities to the subjects leaving his personal priorities. But if Rama had rejected his father's order, would not he had been criticized for ignoring his father's order and non-reliable for his subjects too. Though being called as the incarnation of Vishnu and called as bhagvan Rama, Rama was not able to escape this moral dilemma and ultimately choose to give priority to his father's order. It was not the case that Rama was unaware of the duty of a king. In the Kaschitsarga mentioned in Ayodhyakanda of the *Ramayana*, sitting on the banks of the river Mandakini, Rama asked and guided Bharata his younger brother, the king of Ayodhaya, about the political affairs of the state. Living in exile he still had an attachment and concerns for his Kingdom. His queries were that if the subjects were looked after well or not, if adequate economy had been allotted to meet all the requirements of his subjects or not?

Should Promises Be Always Kept?

The same dilemma could be seen in *Mahabharata* where Bhisma being the only hire of the Kingdom, took a rigorous oath of celibacy for his whole life, so that his father can marry Satyavati. Later when his Kingdom and subjects, dissatisfied of the incompetent rulers, needed Bhisma to become as a king, he refused. To fulfil his oath he refused the general good and centred himself to his individual promises. Till today he is known with the name Bhisma, a person with rigid vows, but the fact can't be ignored that had Bhisma not taken to his vow of celibacy, the war of Kurushatra could have been avoided, which could have saved the life of thousands of people. Amba who was kidnapped by Bhisma pleaded him a lot to get married to her but Bhisma choose his oath, she ended her life, and in next birth was born as Shikhandi. These incidents again raised the moral dilemmas before Bhisma in *Mahabharata.* Was his decision appropriate to believe that his vow of celibacy which he made to his father in a moment of extreme commitment was his ultimate dhrama, keeping at stake his people's welfare. Was not the prevention of a fratricidal war between the brother clain of Pandavas and Kauravas was more important to choose?

And the Dilemma Continues...

In this pandemic times the question of choosing between lives and livelihoods have brought the governments in an ethical dilemma. This problem is international and to choose between them is more difficult. Most of the nations who choose lives before livelihood and went for lockdown, later on faced the problem of economy and hunger and realized that livelihoods were more important than merely saving lives. When WHO declared COVID-19 (SARS-COV-2) as a global pandemic on 11 march 2020, it had already spread in 216 countries globally. The countries which were United States, Brazil, China, Russia, Spain, United Kingdom and India. The New York Times reported at least 4000 more deaths only till March 2020 than the official death rates. India, taking lessons from the situation of other countries, took the decision of the lockdown in the whole country, so that chain of this fatal disease can be broken. But along with this pandemic, it failed to deal with the economic crises. The government was criticized for the lockdown. According to the International Labour Organisation (ILO) around 25 million jobs were lost globally because of this covid situation till the end of 2020. The major providers of employment like the production factories, tour, industry, retail services, small and medium enterprises and education sector, have collapsed making the middle class and BPC to bear the acute brunt of this pandemic. Around 34 nations declared mandatory lockdown, accounting for around 659 million people staying in homes. France, Italy, Iraq, California and Rwanda were pioneer among those countries. Indian government too imposed a nationwide lockdown for 21 days from 24 march 2020, which later on was extended till 31st may in different parts. As a result India was in better position in comparison to other of the world, as the decision of lockdown chosen at the right time had saved lakhs of lives and avoided the worst situations of the pandemic, like in Italy and Britain. During this first wave in 2020, 5% of the affected cases required serious hospitalization and only 1% of them died. But this lockdown had another devastating effect too.

The Choice between Lives or Livelihood?

The jobs and earnings of around 200 million workers including self-employed, salaried workers, laborers and vendors were at stake. In spite of appeal of central and state government to not cut the salaries of the workers during

lockdown and announcement of financial relief packages, the poor labor class suffered from lack of basic requirements like food, gas and money to travel back to their villages. According to economic survey 2020-21, government declared 68,194 crore as fiscal policy response to the pandemic under Pradhan Mantri Garib Kalyan Yojana (PMGKY). But these measures and schemes were too late and too little hence the government was criticized for the pathetic situation and no relief to the small sector enterprises , middle class crises , unemployment , migrate laborers etc. During the 2nd wave of pandemic in 2021 Indian government choose to delay the lockdown this time. The Indian government was again stricken in a dilemma of what to choose this time lives or livelihood. Being the second most populated nation, India is facing the fatal result of this delay. The central government has left the decision on state government to choose lockdown or not. Prioritizing lives for livelihood, most of the government has a 21 day lockdown, which will again result a lasting impact on Indian economy and livelihood. Because of uncertain nature of pandemic and lockdown, the thousands of Migrant laborers, working people and students have starting migrating to their home place. This lockdown has again started the vicious cycle of job loss, slow demand, slump production and poor health infrastructures. But again the government has to face the brutal situation of interrogation and responsibilities towards the citizens.

The dilemma of choosing early lockdown in 2020 or late lockdown in 2021, both are questioned as a balance between saving lines and sustaining the economy both areas to be taken into consideration. Rama can be praised for keeping his promise to his father and become an ideal son but his subjects were deprived of a great ruler from 14 long years. In the same way, on an individual level Bhisma came to be known as a furious firm promise keeper but his priority to subjects rather than his father could have avoided the furious war of Kurushetra. These might be the mythologies which one can find real or full of exaggeration but they teach us a lot.

CONCLUSION

The Road Not Taken

I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.
By Robert Frost

The choice made in the past or in the present, have never been so easy and have been criticized time to time in numerous perspectives. The Indian government is not being criticized for the pandemic but for the response taken by them. The stringent lockdown imposed in 2020 not only destroyed the economy but also forced thousands of people into hunger and poverty and the worst part is that the transmission of this fatal virus still continues. These polices of government not only resulted into economic collapse but also resulted into a devastating humanitarian catastrophe. With lockdown and unlock policies, India in 2021 still continues to struggle with the disease and massive economic losses. The major reason behind it is that India did not learn from the past. The inadequate investment in health sector and the mismanaged containment strategies taken at delayed intervals were another important reasons behind this.

If government had taken into consideration the specific socio-economic contexts in relation to lives of Indians, they could have prevented the situation from getting worst. The lack of educational awareness programmes of this pandemic, overcrowded congested dwellings, lack of physical distancing and lack of official guidelines were the major areas on which the government should have taken strong steps. Along with this major macro-economic strategy, well planned strategies for livelihoods and economy are also required. As the pandemic deepens, India finds itself stucked fully in the dilemma of choosing between lives and livelihoods. May be the experiences of past can provide a clear vision of dealing in this unexpected pandemic situations which could provide better solutions to

deal with the third wave. Whether in Satyuga or in Kalyuga, the authority always has a burden of responsibilities and decisions to be taken, ignoring the individual interest for a larger cause.

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RESEARCH ARTICLE

Comparative Study of an Electro Dry Needling Vs Trigger Point Dry Needling Therapy for Lumbosacral Radiculopathy Patients with Central Sensitization

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ABSTRACT

Lumbosacral radiculopathy is a form of low back pain and known for stubbornness to traditional physiotherapy treatment but many reteaches stated that it responds well to dry needling. Purpose: So author aimed to compare the electro dry needling therapy with conventional dry needling therapy for lumbosacral radiculopathy patients with central sensitization. Subjects: In total, 40 subjects were assigned with randomization to both groups equally so study group (n=20) and control groups (n=20). In the study group, electro dry needling treatment was administrated using solid filiform needles while the control group received trigger point dry needling followed by the high-frequency current. Pain and Central sensitization were measured by numerical pain rating scale (NPRS) and Central sensitization inventory-Gujarati (CGI) respectively at beginning of the study and the end of 2nd-week of treatment. Conclusion: As per the result of data analysis there is a significant (P>0.05) difference (Improvement) in CSI score and NVAS score of subjects treated with Electro Dry needling therapy. Electro dry needling is proven as, the choice of non-medicinal treatment of Central sensitization and pain which mainly have the association with depression and anxiety that amplifies the symptomatology.

Keywords: central sensitization, electro dry needling, Lumbosacral radiculopathy, trigger point dry needling

INTRODUCTION

Lumbosacral radiculopathy is a specific type of back pain that is one of the commonest health conditions worldwide and is highly associated with disability, emotional changes, and work absenteeism [1-3]. Given that lumbosacral radiculopathy is very prevalent, the treatment costs associated with this condition are very high. [4,5] Approximately 60% of patients consider themselves not recovered in 1 year from the onset of symptoms, with moderate levels of

pain and disability persisting over time.[6,7] Therefore, many of these patients become frequent users of health care services to find treatments to minimize the severity of their symptoms. Central sensitization is described as per the International Association for the Study of Pain as "*Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input."[*8] Central sensitization is also defined as "an augmentation of responsiveness of central neurons to input from unimodal and polymodal receptors."[9]

Trigger points can persuade central sensitization which is supported by emerging research as it demonstrated physiological links amongst the clinical manifestations of trigger points, e.g. hyperalgesia, referred pain, allodynia, and central sensitization. Although the fundamental mechanisms are still required to explore. Mense suggested that trigger points activate a peripheral nociceptive afferent barrage into the central nervous system, the presence of multiple trigger points at the same place or different places can maximize its effects on spinal cord neurons and supra-spinal structures [10]. The mechanism of the rapid decrease in local and referred pain associated with trigger point dry needling which is often observed in musculoskeletal rehabilitation. The steadfastness of trigger point associated with referred pain is can be related to the decrease in the nociceptive input to dorsal horn neurons of the spinal cord, and stoppage of the spread of pain and central sensitization. The positive response to trigger point dry needling therapy on referred pain can work on central sensitization to reverse symptoms [11]. Literature published by Srbely et al. suggesting that trigger point can result from central sensitization and they hypothesized that pain arising from a trigger point may be caused by neurogenic mechanisms secondary to central sensitization. [12]

Implications for Clinical Practice

Current data support the trigger points can produce central sensitization and which commonly associated with many chronic pain conditions. So clinically it is very important to address trigger points effectively to neutralize them and get rid of chronic or persistent pain. Adequate trigger points management can prevent and reverse the development of spatial pain spread in chronic pain conditions. Inactivation of a trigger point is associated with attenuation of central sensitization [13–15] and induction of spinal inhibition [16, 17]. Many dry needling approaches have been developed based on different individual theories, insights, and hypotheses. [18-21] Trigger point model specifically targets myofascial trigger points. [18-21] Trigger point dry needling has been shown to alter the biochemical environment surrounding myofascial trigger points.[22,23] A recent Cochrane review concluded that when dry needling is added to other conventional physiotherapy exercises, then it is more effective at relieving neuro-musculoskeletal pain than conventional therapies alone in non-specific low back pain [24, 25]. In this context, the present study intended to verify the outcome of Electro dry needling against Conventional trigger point dry needling as a primary treatment intervention in a subject with lumbosacral radiculopathy.

METHODS

Patients: Outpatients aged 40–60 years with lumbosacral radiculopathy were recruited from the Akshar Clinic, Vadodara with inclusion criteria of lumbosacral radiculopathy for 3 months or longer with positive lasegue sign; (2) no sign of cauda equine; and exclusion criteria: (1) major trauma or systemic disease; and (2) receiving conflicting or ongoing co-interventions, (3) subject contraindication to interventions, (4) Having specific conditions such as fractures, neoplasm, spondylolysis, spinal stenosis, spondylolisthesis, ankylosing spondylitis, and previous low back surgery. Risks and potential complications were discussed with the subject and consent was given to proceed with the intervention. Complications that may occur post electro dry needling / dry needling include muscle soreness, bruising, fatigue, and vasovagal reaction. Potential but rare complications post needling include infection, a stuck or broken needle. There were no subject contraindications to intervention, such as local infection, history of immune suppression (e.g., cancer) or bleeding disorders (e.g., hemophilia), high anti-coagulant use, pregnancy (especially first trimester), compromised or questionable equipment sterility, denied subject consent, and inadequate practitioner practical knowledge. The Institutional Ethical Committee of Akshar Clinic, Vadodara, had approved the

research protocol. All enrolled patients gave their written informed consent, and all procedures were conducted per the Declaration of Helsinki.

Design

It was a randomized controlled trial, a single-blind study where subjects enrolled into two equal groups i.e either the experimental group (n=20) or the control group (n=20).

Treatment Procedure

The following muscles were treated bilaterally during all treatment sessions.
Multifidus at L1 – L3- L5 level,
Erector spinae,
Piriformis and
Soleus Muscle.

The monofilament needle used was 0.25 mm in diameter and was held by the therapist's dominant hand. After skin inspection and disinfecting with 70% isopropyl alcohol, the needle was inserted utilizing a clean technique. The needle was inserted into the skin just above the taut band over the palpable trigger point. Once the needle was inserted into the skin tissue, it was directed into the targeted trigger point of a specific muscle. The needle was manipulated up and down in a rapid frequency at a rate of approximately 1-2 strokes per second without fully withdrawing the needle from the skin. This up and down Piston movement of the needle is intended to induce a local twitch response (LTR). As soon as the needle was pulled out of the skin, the needle insertion site was compressed firmly for a minimum of three seconds, and the needle was discarded into a sharps container. Due to the chronic nature of the subject's symptoms, the decision was to leave the needles within the target muscles for 10 minutes. And this procedure is followed by the application of high-frequency current. And in electro dry needling needles have inserted with same procedure and then it collected to 4 channel TENS via crocodile electrodes for 10 minutes where Needles work as an electrode to conduct an electrical impulse deep within the muscles and produce repeated muscular contractions during treatment. Each patient received a total of five treatments per week for 2 weeks, and follow-up was measured at the end of 2nd week. Following the treatment interventions, the subject of both groups was given follow-up instructions to minimize post-needling complications. Subjects were educated to have rest, apply ice and maintain hydration throughout the next 24 hours.

Outcome Measures

CS is measured with CS inventory- Gujarati (CGI) [29] having 25 questions which can be quantified on a score of 0-100. A score above 40 indicates the presence of CS. Pain intensity quantified with an 11 point numerical pain rating scale (NPRS). [30]

Statistical Analysis

Analysis was done by using SPSS-16 software and Microsoft excel. Demographic Profile: The age of all subjects was recorded for geographic data analysis as shown in table 1. Alpha level was set at 0.005 for 99% CI and we found difference not significant in mean age. All the subjects completed the entire study protocol as defined, by 2 weeks in the treatment sessions. Pre-test and post-test values of CSI score (Table 2), NVAS (table 3) scores were measured. To compare the pre and post-treatment effects between the groups, an unpaired t-test was used. Alpha level was set at 0.05 for 95% CI.

RESULTS

As per data analysis, there is a significant difference (Improvement) in CSI score and NVAS score of subjects treated with Electro Dry needling therapy.

DISCUSSION AND CONCLUSION

From the results, it is clear that there is a significant difference in CSI score and NVAS score of subjects treated with Electro Dry needling therapy compare to conventional trigger point dry needling therapy in subjects with lumbosacral radiculopathy. This can be due to the use of the needles as electrodes offer many advantages over more traditional transcutaneous nerve stimulation (TENS). [21] The use of electro needling can bypass the resistance of the skin to electrical currents so it provides better analgesic effects and improved functionality than conventional TENS.[26,27] D-aspartate (NMDA) receptor on the central terminals of the dorsal root ganglion appears to play an important role in the development of central sensitization related to persistent inflammatory pain.[28] Electro dry needling is proven as, the non-medicinal treatment of Central sensitization which mainly has the association with depression and anxiety that amplifies the symptomatology.

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Conflicts of interest
There are no conflicts of interest.

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Table 1: Demographic details

AGE	A	B
mean	53.85	54.2
SD	10.03	9.78
N	20	20

Table 2: Between Group Analysis- CSI

Difference	-5.700
Standard error	2.717
95% CI	-11.1997 to -0.2003
t-statistic	-2.098
DF	38
Significance level	P = 0.0426

Table 3: Between Group Analysis- NVAS	
Difference	-2.100
Standard error	0.451
95% CI	-3.0130 to -1.1870
t-statistic	-4.656
DF	38
Significance level	P < 0.0001

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RESEARCH ARTICLE

In-vitro Screening of Anti-Cancer Activity of Leaves and Flowers of *Quisqualis indica* Linn by using Hela Cell Lines

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ABSTRACT

Cancer is a group of diseases caused by loss of cell cycle control. Cancer is associated with abnormal, uncontrolled cell growth. The present study was aimed to evaluation of the *In vitro* anticancer activity of the leaves and flowers of *Quisqualis indica* Linn on the *HeLa* cell line. The cytotoxicity of ethanolic extract of *Quisqualis indica* Linn **o**n *HeLa* cell line were evaluated by the 3-(4,5-dimethythiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Ethanolic extract of *Quisqualis indica* Linn has a significant cytotoxicity effect on Hela cell line in a concentration range between 6.25 and 100 µg/ml using MTT assay .The Percentage viability was found to be 87.67%, 73.97%,63.01%, 32.67%, and23.28% toxic in *HeLa* cell line . Inhibitory concentration 50 (IC50) value of Ethanolic extract of *Quisqualis indica* Linn of on *HeLa* cell was found by MTT assay 30.437 µg/ml. The results obtained from the *In-vitro* studies performed using *HeLa* cell lines reveals that the ethanolic extract of *Quisqualis indica* **Linn** has good anticancer activity. So, this medicinal plant possess significant cytotoxicity activity.

Keywords: Cytotoxicity activity, 3-(4,5-dimethythiazol-2-yl)-2,5- diphenyltetrazolium bromide assay,, *HeLa* cell line.

INTRODUCTION

Cancer is a disease that has always been a major threat and has been characterized by proliferation of abnormal cells. Currently, chemotherapy and radiotherapy treatments were followed for the treatment of various cancers but are found to be having limited survivability and possess various side effects. Medicinal plants represent a vast potential source for anticancer compounds and support the immune system, thus improving body resistance to the disease

and its treatments. Many Indian species and plants are useful in different types of cancer (Renjini Haridas *et al*., 2016.).The Plant *Quisqualis indica* Linn is used as anti anthelmintic to expel parasite worms (especially in children) or for alleviating diarrhoea. Used for gargling. Also used in combat nephritis. Used to treat rheumatism. It is anti-pyretic, anti-inflammatory, immunomodulatory, anti-staphylococcal, anti-oxidant.(The Wealth of India 2005). Decoctions of the root, seed, or fruit can be used as anti anthelmintic to expel parasitic worms or for alleviating diarrhoea. The fruit are also used to combat nephritis. Leaves can be used to relive pain caused by fever. The roots are used to treat rheumatism. Flowers are used to relive headache.

Collection and authentication of plant material

The leaves and flowers of *Quisqualis indica* Linn. Were collected from Thanjavur in the month of March-2019. The plant has been taxonomically identified and authenticated by the Botanist Dr. A. Balasubramanian. The authenticated plants were used for preparation of extracts. The authenticated plant was used for the preparation of the extracts. (Basset, J *et al*., 1985).

Preparation of the extract

The leaves and flowers of *Quisqualis indica* Linn. Were collected and air dried under shade and then coarsely powdered with the help of mechanical grinder. The powder was passes through Sieve No.40 and stored in an airtight container for the extraction. The collected, cleaned and powdered leaves and flowers of *Quisqualis indica* Linn. Was used for the extraction purpose. 300grms of powdered material was evenly packed in the Soxhlet apparatus. It was then extracted with various solvents from non-polar to polar such as petroleum ether, aqueous and ethanol. The solvents used were purified before use. The extraction method used was continuous hot percolation and carried out with various solvents, for 72 hours. The aqueous extraction was carried out by cold maceration process.

Method of extraction

Continuous hot percolation process.

Requirements

Shade dried coarse powder of leaves and flowers of *Quisqualis indica* Linn.
Soxhlet apparatus.

Solvents used

- Petroleum ether.(60-80°C)
- Alcohol 90%v/v.(75-78°C)
- Distilled water

Preliminary phytochemical studies

The extracts obtained (Pet.ether, ethanol and aqueous) was subjected to the following preliminary phytochemical studies. (Kokate C.K,Kokate C.K)

Evaluation of *In vitro* anticancer activity

Experiment

The *In-vitro* anticancer activity of ethanolic extracts of *Quisqualis indica* Linn against human cervical cancer cell line (HeLa).

Requirements

The human cervical cancer cell line (HeLa) was obtained from National Centre for Cell Science (NCCS), Pune.

Invitrogen Reagents

The cell line was cultured in 25 cm2 tissue culture flask with DMEM supplemented with 10% FBS, L-glutamine, sodium bicarbonate and antibiotic solution containing:

- Penicillin (100U/ml)
- Streptomycin (100µg/ml)
- Amphoteracin B (2.5µg/ml)
- Cultured cell lines were kept at 37ºC in a humidified 5% CO2 incubator

Cell Treating Procedure

Cells seeding in 96 well plate: Two days old confluent monolayer of cells were trypsinized and the cells were suspended in 10% growth medium, 100µl cell suspension (5x104 cells/well) was seeded in 96 well tissue culture plate and incubated at 37ºC in a humidified 5% CO2 incubator. (Harbourn, J.B.1976).

Preparation of plant extracts and compound stock: 1 mg of each plant extract or compound was added to 1ml of DMEM and dissolved completely by cyclomixer. After that the extract solution was filtered through 0.22 µm Millipore syringe filter to ensure the sterility.(Fulya Tugbaartun *et al*., 2017)

Antiproliferative effect Evaluation: After 24 hours the growth medium was removed, freshly prepared samples in 5% DMEM were five times serially diluted by two fold dilution (6.25µg, 12.5µg, 25µg, 50µg, 100µg in 100µl of 5% MEM) and each concentration of 100µl were added in triplicates to the respective wells and incubated at 37ºC in a humidified 5% CO2 incubator. (Rajesh M *et al*., 2011, Ackermann, *et al* .,1955).

Antiproliferative effect by Direct Microscopic observation: Entire plate was observed at an interval of each 24 hours; up to 72 hours in an inverted phase contrast tissue culture microscope (Labomed TCM-400 with MICAPSTM HD camera) and microscopic observation were recorded as images. Any detectable changes in the morphology of the cells, such as rounding or shrinking of cells, granulation and vacuolization in the cytoplasm of the cells were considered as indicators of cytotoxicity. (Chinami, M., *et al* 1986.,Vogt. M., *et al* 1958)

Antiporliferative effect by MTT Assay: MTT is a yellow water soluble tetrazolium salt. A mitochondrial enzyme in living cells, succinate –dehydrogenase, cleaves the tetrazolium ring, converting the MTT to an insoluble purple formazan. The amount of formazan produced is directly proportional to the number of viable cells. (Patel S et al., 2017, Moustafa MA *et al*., 2014). After 24 hours of incubation, 15µl of MTT (5mg/ml) in Phosphate Buffered Saline (PBS) was added to each well and incubated at 37ºC for 4hours. The medium with MTT was then flicked off and the formed formazan crystals were solubilized in 100µl of DMSO and then measured the absorbance at 570nm using micro plate readed. The % cell viability was determined using the following formula and graph was plotted between % growth inhibition and concentration and from this IC50 was calculated.

The percentage of growth inhibition was calculated using the formula:

$$\% \text{ of viability} = \frac{\text{Mean OD Samples x } 100}{\text{Mean OD of control group}}$$

RESULTS AND DISCUSSIONS

In this study, the *In-vitro* conformation of their toxicity on human cervical cancer cell line (*HeLa*) was studied using MTT assay. The cytotoxicity study was carried out for plant ethanolic extract of the leaves and flowers of *Quisqualis indica* Linn. The ethanolic extract was screened for its cytotoxicity against human cancer cell lines (HeLa) at different concentrations to determine the IC50 by MTT assay. Cytotoxicity of ethanolic extract of the leaves and flowers part of *Quisqualis indica* Linn against *HeLa* cell was found to be 87.67%, 73.97%, 63.01%, 32.67% and 23.28% percentage viability at a concentration of 6.25, 12.5, 25, 50 and 100 µg/ml. IC50 value of 30.437 µg/ml was obtained for human

cervical cancer cell line (*HeLa*). This was presented in the table 1,2 and figure no1,2. The percentage growth inhibition was found to be decreasing with increasing concentration of test compounds. This showed that the extracts possess an *In-vitro* anticancer activity against tested Hela cell line. On preliminary screening, Ethanol extract found to be more active and shows good cell inhibition activity against the cell lines tested. The Ethanolic extract of *Quisqualiss indica* Linn has significant cytotoxicity effect on Hela cell line. The IC50 value and R2 value was 30.347 μg/ml and 0.9683 μg/ml, respectively.

CONCLUSION

The results obtained from the *In-vitro* studies performed using *HeLa* cell lines reveals that the ethanolic extract of *Quisqualis indica* Linn has good anticancer activity. So, this medicinal plant possess significant cytotoxicity activity. Further investigation, *In-vivo* experiments are required to prove the mechanism of action of the plant extract.

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ABBREVITATIONS

MTT - 4,(5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide.
HELA - "Helen lane'' or "Helen Larson"
DMEM - Dulbecco s modified eagle s medium
IC 50 - Half maximal inhibitory concentration

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Table no 1: *Invitro* cytotoxicity studies on Ethanolic extract of *Quisqualis indica* Linn in *Hela* cell line

S.No	Concentration (µg/ml)	Absorbance			Average
		Response 1	Response 2	Response 3	
01	Control	0.754	0.723	0.707	0.728
02	6.25	0.628	0.616	0.688	0.644
03	12.5	0.589	0.516	0.523	0.542667
04	25	0.425	0.476	0.483	0.461333
05	50	0.255	0.258	0.217	0.2433333
06	100	0.116	0.202	0.196	0.171333

Table no 2: *In vitro* cytotoxicity studies on Ethanolic extract of *Quisqualis indica* Linn in *Hela* cell line.

S.No	Conc (µg/ml)	Percentage Viability	IC_{50}	R^2
01	6.25	87.67%	30.347µg/ml	0.9683
02	12.5	73.97%		
03	25	63.01%		
04	50	32.67%		
05	100	23.28%		

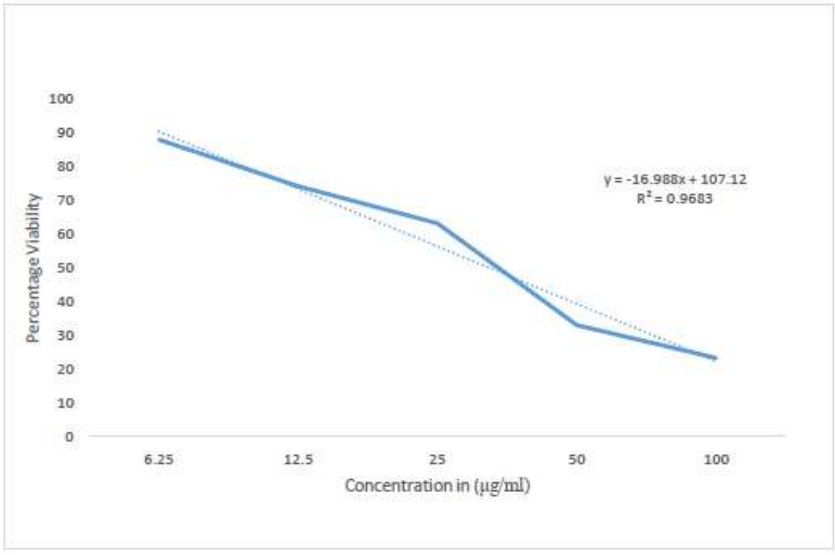

Fig 1: *In vitro* cytotoxicity studies on Ethanolic extract of *Quisqualis indica* Linn in HeLa cancer cell line.

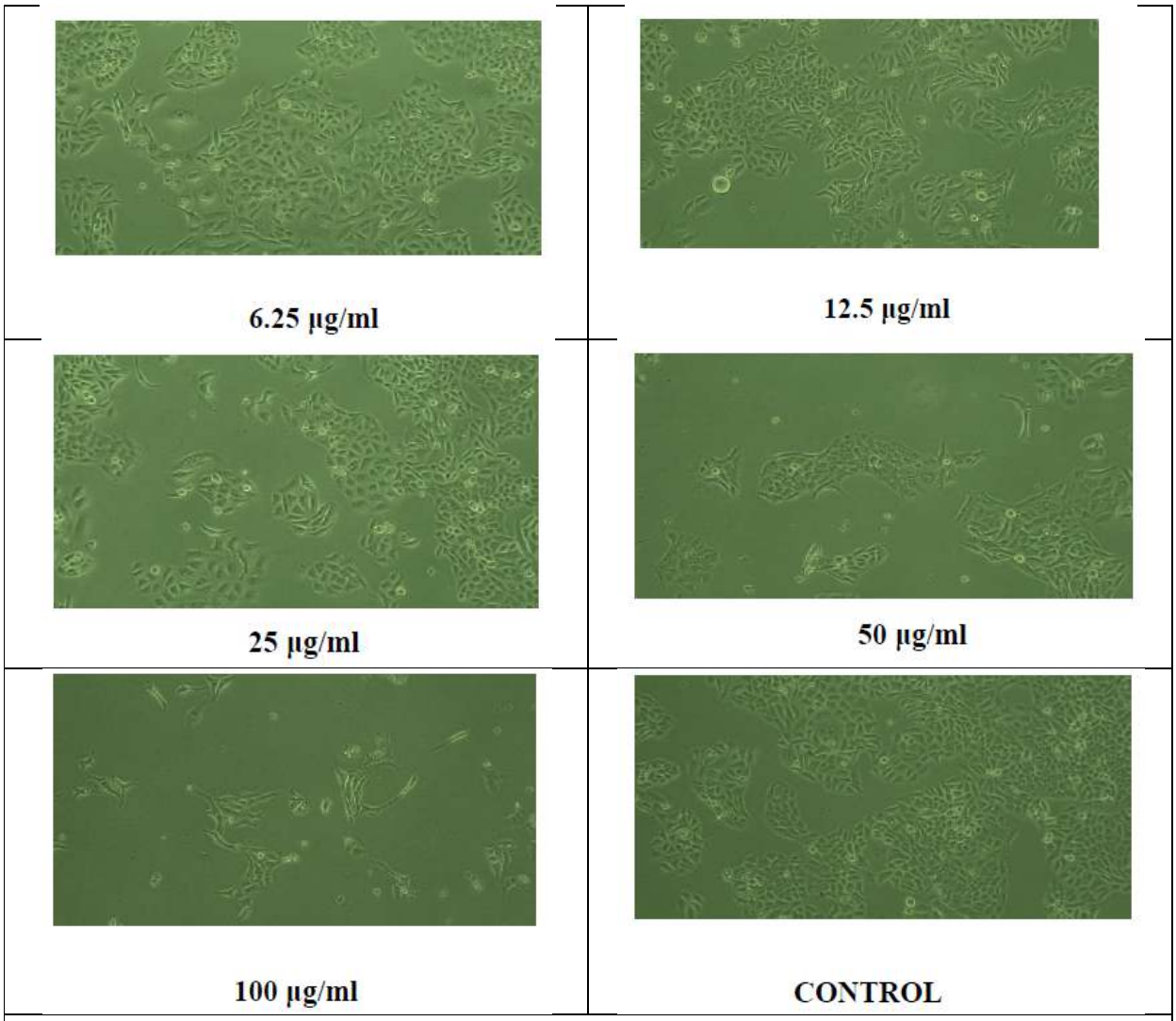

Fig 2: Anticancer activity on *HeLa* cell line in ethanolic extract of *Quisqualis indica* Linn

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RESEARCH ARTICLE

A Study on Innovation and Technology for Transforming Education: Emerging Trends and Impact

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ABSTRACT

Innovation is changing instruction in a way that powerfully includes understudies by supplanting an educator focused model with an understudy focused one. Such intelligent exercises can be combined with the understudy reaction frameworks that make it natural for understudies to address questions and participate in exercises. Computerized change is that the way toward utilizing advanced advances to form new or adjust existing business cycles, culture, and client encounters to satisfy changing business and market necessities. This reconsidering of business within the computerized age is advanced change. It transcends standard positions like arrangements, advancing, and customer care. All things considered, computerized change starts and finishes with how you contemplate, and attract with, clients. As we move from paper to bookkeeping pages to keen applications for handling our business, we get the chance to rethink how we work together how we attract our clients with computerized innovation on our side. Instructors from all grade-levels are coming to grasp the benefits of innovation within the homeroom. Ordinarily, training is one among the last enterprises to roll out broad improvement, clutching out of date strategies and practices. In this paper, the different pattern in modern education system framework is examined.

Keywords: Innovation, Education, Digital transformation, Social media learning, AR, VR

INTRODUCTION

Digital Transformation in Education

Computerized change has been among the top innovation patterns in training for quite a long while at this point, similarly as it has been across pretty much every industry. As of not long ago, progress toward this sort of change has been delayed in the training area, with conflicting practices, strict financial plans, and absence of a bound together arrangement among the most glaring explanations behind the deferral. However, through the advanced change and the ascent of instructive innovation, educators have started rolling out uncommon improvements to their guidance, appraisals, even the actual make-up of their study halls, and at a lot quicker rate than anticipated. For independent companies simply beginning, there's no compelling reason to set up your business measures and change them later. You can future-confirmation your association from the word go. Building a 21st-century business on stickies and manually written records simply isn't maintainable. Thinking, arranging, and building carefully sets you up to be spry, adaptable, and prepared to develop and several opportunities are mentioned as fig.1. Advanced change implies changing an association's center business to all the more likely address client issues by utilizing innovation and information. In training, that target client is frequently understudies, however it could likewise be workforce, staff, graduated class, and others with various scopes represented in fig. 2.

Computerized change pointed toward changing the understudy experience may incorporate things, for example,

- Recruiting understudies carefully, utilizing web-based media and text informing as a feature of an information driven choice interaction.
- Allowing understudies to enlist through their cell phones on adaptable cloud-based understudy data frameworks.
- Providing an assortment of internet learning alternatives so understudies have enough courses to browse at key focuses in their scholarly vocation.
- Working with personnel and projects to change courses over to flipped and mixed models;
- Using innovation to screen understudy progress and achievement measurements and execute intercession conventions.
- Partnering with industry to give computerized identifications and authentications to upgrade vocation openings.

Emerging Trends in Education Technology

Collaborative Learning: Innovation has made it workable for everybody to remain associated. We interface, talk about and institute upon circumstances cooperatively. This shared methodology has acquired significance in the learning cycle too. In a study hall learning model, instructors support coordinated effort by relegating bunch exercises and errands. At the point when understudies group up together to chip away at a project or take care of an issue, it assembles their shared abilities. Cooperating works on their arrangement and builds commitment as represented in fig.3. In spite of the fact that eLearning is very mainstream, it incorporates cooperation with highlights to share and talk about. In a conventional showing model, an educator enters a homeroom, represents around 30 minutes, and leaves when the chime rings. However, today, innovation has overcome any issues among instructors and understudies. Instructors are undeniably more open now and go about as coaches to help understudies in their general turn of events. This community learning approach assists understudies with cooperating with their friends and assemble their relational abilities.

Learning Outside the Classroom Environment: Versatile based gadgets have taken learning outside of the study hall as represented in fig.4. With mobile Learning and eLearning filling in prevalence, understudies can learn at their own speed and time. This pattern is relied upon to keep up as it is a helpful technique for conveying just as getting the schooling. Planning portable first responsive substance assists understudies with going through their courses whenever and anyplace. Web association is presently not an issue with disconnected understanding abilities.

Digital books can be implanted with many highlights to improve the learning experience. Complete with explanation instruments, bookmarks, hyperlinks, word reference, search include, an eBook makes learning more adaptable. The greater part of the instructive foundations today has received portable learning into their learning biological systems, profiting understudies and instructors the same.

Social Media in Learning: With kids as youthful as eleven having online media profiles on different stages, you can't actually hope to get them far from web-based media for a really long time. Along these lines, instructors figured out how to use this pattern and transform it into a useful asset for improving the learning process. Educational foundations have begun utilizing web-based media as a specialized apparatus, where understudies can cooperate with their companions and employees. Normally, understudies share recordings and pictures with their companions and supporters. However, with social highlights implanted in their eBooks, they can share study materials, conclusions, projects through the various social media as in fig.5. They can remark on another person's post or offer connects to different sites, meanwhile assembling peer organizations and improving the web-based learning experience. Instructors permit the utilization of web-based media as a component of the learning model since it assists understudies with remaining intrigued by their course and expands commitment. Online media is staying put and fusing it into learning modules will assemble a culture of joint effort and sharing, prompting a further developed learning experience.

Interactivity in Classroom: Carrying innovation into the study hall has made homerooms exuberant and intuitive. With eBooks, the course content can be inserted with recordings, increased reality, sound documents and so forth in contrast to a printed book, eBook considers more connection to occur in the study hall. The flipped study hall model has permitted understudies to do all the learning at home and all the down to earth work at school. All these new innovations have achieved an adjustment of the way that classes used to work generally. Educators would now be able to help and guide understudies with their schoolwork in class. They can have conversations and exercises in study halls, establishing an intuitive climate where understudies are totally associated with the learning cycle through the interactive sessions as represented in fig.6. Making communication and commitment has become a need for some schools and colleges. This way of learning has seen a development as of late for its capacity to keep understudies occupied with the homerooms.

Data Management & Analytics: Overseeing information has gotten helpful and significant with the coming of innovation in the schooling framework. Instructors would now be able to have total investigation of an understudy's presentation, for example, the quantity of tests endeavored, sections finished and so forth Schoolwork and tasks can be allocated to the whole class without a moment's delay and instructors can assess the outcomes on the web as shown in fig.7. This sort of computerization in homeroom exercises has empowered instructors to zero in additional on their course modules and offer inside and out direction. Investigation has become a significant piece of any internet learning model as it empowers the estimation of a kid's commitment and scholarly execution. As per the information accessible, educators can foster activity intends to work on understudies' presentation. In the event that the information uncovers an aggregate issue or an alarming example with an individual understudy's presentation, it very well may be featured, and fitting measures can be taken. The distant observing of understudy exercises empowers instructors to offer customized preparing whenever required. This load of components has added to making information the executives and information examination a significant piece of schooling.

Immersive Learning with AR and VR: With the presentation of expanded reality and augmented reality into the instruction framework, the study hall learning experience has gone through a colossal change. Learning has gotten substantially more vivid than conventional strategies. In contrast to plain pictures and active trials in the lab, understudies would now be able to see improved renditions of the picture and articles on their cell phones as represented in fig.8. The expanded and computer-generated reality patterns in training innovation are making learning a convincing encounter. While expanded reality gives an improved perspective on a genuine picture, computer generated reality gives a bogus impression of reality around them. Both these procedures have taken

advanced figuring out how to new measurements. AR and VR are progressively being utilized to clarify complex ideas.

Gamification in Education: This pattern has been acquiring fame for the basic explanation that it expands understudy commitment. We have seen gamification being utilized in study halls in various structures, for example, leaderboards, reward focuses, identifications, stickers and so forth of the relative multitude of patterns in schooling innovation, gamification is the one pattern which ensures an expansion in cooperation, commitment, and contest mentioned in fig.9. Understudies become effectively engaged with the study hall exercises to build their scores and leaderboard rankings. Also, the need to lead the scoreboards bring about further developed execution and better maintenance. Gamification boosts understudies to learn and work on, further developing the general learning measure. Along these lines, educators use gamification as a way to build commitment, support inspiration and establish an intuitive homeroom climate. In any case, it is useful in expanding understudies' assurance and urges them to perform better without fail. We can see this pattern being used further, in more inventive approaches to upgrade the learning model.

Online Data and Cybersecurity: The requirement for information security is at an unsurpassed high. While distributed storage has become the standard nowadays, it could demonstrate sad now and again. Individuals and foundations incline toward distributed storage since it is a common climate and it makes getting to information simple for everybody. So, there have been a great deal of examples in the past where online information has been hacked for emancipate. Digital dangers have been a reason for stress for some foundations instructive and something else as fig.10. Understudy data like name, email address, date of birth and telephone numbers can't be compromised. Test outcomes and tasks are additionally put away on the cloud by many.

Training establishments are executing the best information safety efforts to secure their online information and their understudies' advantages. While we are at the subject of cybercrimes, we should likewise address cyberbullying. Cyberbullying could prompt perilous results, and consequently schools and colleges are taking suitable careful steps to forestall web-based harassing. Online protection, accordingly, is one pattern which holds a ton of significance during circumstances such as the present. It was inevitable before the schooling area was taken over by innovation. Albeit the acknowledgment rate was low first and foremost, it progressively acquired energy. Instructing and learning techniques have gone through a huge change because of the relative multitude of patterns in training innovation. Consistently, recent fads arise to give something new to the students. They say change is steady, comparatively, advancements in the field of innovation are likewise consistent. Furthermore, certain advancements can be executed in the instruction framework for working on their learning and improvement measure. The aftereffect of these developments become a pattern which then, at that point prompts better instructing and learning strategies.

RESULTS AND DISCUSSION

These days, understudies become increasingly more associated with shaping their own schooling. In 10 years, understudies will fuse such a lot of freedom into their learning interaction, that tutoring will become crucial to understudy achievement. Furthermore, instructors will frame an essential issue in the wilderness of data that understudies will clear their direction through. I truly accept that the fate of innovation in instruction is tied in with adjusting to the quick evolving world, offering understudies a chance to pick their own specific manner of getting the hang of, joining hypothesis and practice, continually considering the current interest of the market. Despite the fact that there is still vulnerability in the training area, thorough advances are being taken to smooth out the interaction and make schooling available to understudies having a place with all social and gatherings of people. There is likewise a positive change in the course of fairness and variety. With innovation offering arrangements at a colossal speed, it seems as though things will just improve from here.

FUTURE SCOPE

Web based learning and present-day developments have achieved a significant change in the manner society and understudies see instruction. Join that with innovation and we have another instructional method structure for the Indian schooling framework. A few improvements are normal in the schooling segment regarding understudies, educators, getting the hang of/showing techniques, and organizations. The center focuses are:

1. Understudies' schedule will be intended to set them up for the continuous advanced time through openness to key innovations that are molding the world we live in.
2. Computerized reasoning, Machine Learning, Virtual and Augmented reality, and Big Data will assume a significant part in this trendy training system. Coding and computational reasoning abilities will be advanced so understudies have assorted profession alternatives before them.
3. Arrangements in the instruction area will be gainful on a worldwide scale. As the world retreats to the advanced mode for sharing arrangements and thoughts, training hence will advance vocation destinations and objectives, and different practices and strategies that focus on the worldwide crowd.
4. The proposed changes will reflect in the manner we assess public, private, and advanced education foundations, and assist with executing an understudy centered structure that will overcome any issues among territorial and sub-region establishments.
5. Since the pandemic drove digitization into the instruction area, far off learning turned into a standard for over 1.5 billion understudies on the planet. Almost 92% of Indian residents invited this as a positive change.
6. Another huge change will be the transformation of mixed or half breed learning practices to offer a more adaptable and effective arrangement of training. This will incorporate web based showing methods, e-courses, and learning applications as computerized schooling stretches out its extension to incorporate at-home learning administrations.
7. Cooperating with content creation offices will guarantee advanced substance is given in a different scope of dialects, further boosting the development of India's EdTech area.
8. Homeroom time, then again, will be held for viable work, conversations, and contextual investigations. The new instructive program has imagined a vivid learning experience for homerooms using skilled innovations.
9. A solid spotlight on extracurricular exercises and science, expressions, and arithmetic clubs will advance a for the most part uplifting outlook towards training and effect the general improvement of understudies.
10. Sports and expressions will be advanced as standard choices rather than elective subjects. This will bring about more inspiration and commitment from understudies who will have more noteworthy command over their vocation decisions. Utilizing psychometric investigation will likewise assist with deciding equipped areas for understudies to seek after.
11. Compelling professional preparing designated at creating industry-related abilities and aptitude will be commanded to help understudies land truly amazing jobs.
12. Instructive organizations are currently setting more accentuation on instructors' upskilling and preparing to work with the advancement of adaptable and further developed educating rehearses.

These reformative changes request to be executed effectively with full collaboration from aggregate government bodies for a compelling on the web instructive design to drive developments in the Indian Education System.

CONCLUSION

Eventually, we realize that there is a great deal to process when we talk about instructive innovation patterns. In any case, remember that innovation has saturated training and recharged its entire educating and learning measure. Particularly eLearning, an instructive apparatus that not just expands the openness and accommodation of training yet additionally changes the learning practices and students' cravings for learning. These 8 innovative methodologies have changed the whole customary way to deal with schooling. In basic words, innovation has furnished educators and students with another and upgraded method of collaborating during the learning interaction. Nonetheless, innovation actually stays an empowering agent and its reception will be more powerful related to a viable learning

system and an association wide learning society; particularly when organizations need to reinforce their labor force's delicate abilities, similar to correspondence, client care, and so forth Furthermore, combined with these most recent learn-tech patterns, associations remain to accomplish further developed learning commitment and higher efficiency over the long haul.

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Fig 1: Opportunities for Digital Transformation

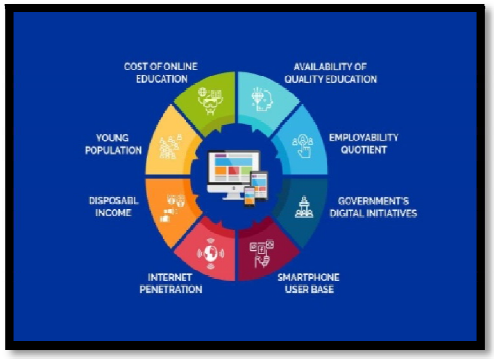

Fig 2: Scope of online Digital Education

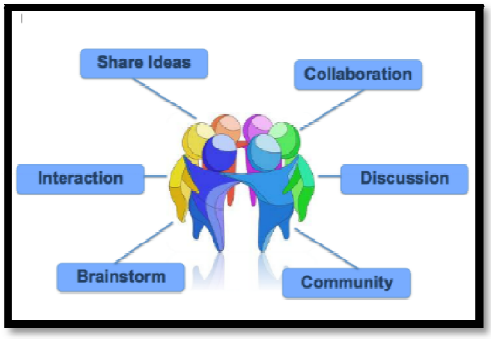

Fig 3: Collaborative Learning

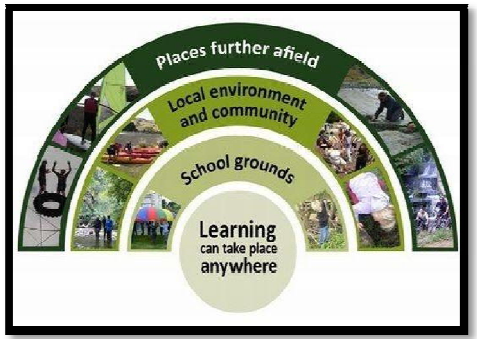

Fig 4: Learning Outside the Classroom Environment

Fig 5: Social Media in Learning

Fig 6: Interactivity in Classroom

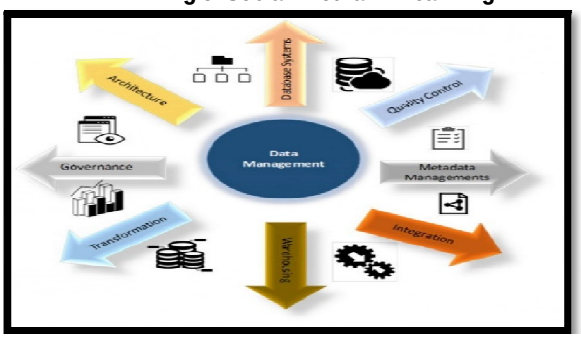

Fig 7: Data Management & Analytics

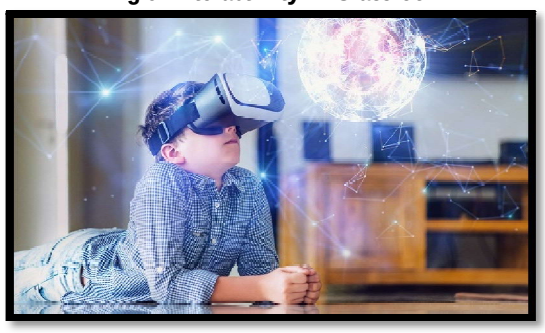

Fig 8: Learning with AR and VR

Fig 9: Gamification in Education

Fig 10: Data and Cybersecurity

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REVIEW ARTICLE

An Improved Plants Disease Prediction System Based on Ann Approach: A Review

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ABSTRACT

Indian Agriculture has major part in Indian Economy. After development and adoption of new technologies our farming will be smart farming, is the need of our farmers. There are many new adoptions in agriculture sector. Major challenge in the agriculture sector is plant diseases and destructive insects. Earlier prediction of plant diseases in crops could help early treatment and also reduce economic losses. Several researchers proposed machine learning techniques to predict plant diseases. In this review paper we will study and compare existing plants disease prediction system technologies and will see the future possibilities for researchers.

Keywords: Image processing, Plant disease detection, Classification, Leaf disease.

INTRODUCTION

The growth of a country depends on its business and also agriculture. Agriculture provides food and raw materials to the human and food industry. Food is essential need of human and plant diseases are big issue for farmers, it can be happened any time between sowing and harvesting. Plant disease does huge loss to crop and economy. Hence disease detection plays an important role in agriculture. Researchers done their study on different plants leaves like tomato, potato, rose, beans, lemon, banana etc. Machine learning allowed researchers to improve the prediction, detection and recognition system. Traditional method for leaf disease detection was only empty eye observation by human. Machine learning can be used for detecting diseases on plants. Machine learning is one of the sub parts of Artificial Intelligence to work automatically or give instructions to do a particular work. In machine learning we

have to train the data and fit that trained data into models that it will result in useful information to the human. For the classification we can use colors of leaves, damaged number of leaves, and area of the unhealthy plant leaf. For best accuracy we overviewed different authors with machine learning algorithms to identify different plant leaves diseases. Image acquisition, image preprocessing, image segmentation, feature extraction and classification are the different level of image processing [40-45].

Plants fulfill the essential needs of human as well as animals like food, shield, building material, ayurveda medicines, fuels, woods etc and also minimize the air pollution. Environment should be protected by the human from problems n caused by floods, fire, human development etc. Cultivation of plants is important as it gives us the different types of fruits, vegetables, grain, nuts and medicines. We need wood for the construction purpose, furniture, for making paper etc. Bio-fuel production can be done by the decaying of plant as it forms the fertilizer, also used for generating the electricity. The agriculture field deals with many difficulties the big one is losses in crop yield. It affects the economy of the country. Because of plant diseases the quality and also the quantity is being affected. There are many diseases in agricultural plants, if we can control it than we will control the production of wastage. Due to these reasons it will be good to detect diseases timely. Many different methods are there to check diseases are man base and technology base checking. Some diseases can be seen by human eyes. The plant diseases like pathogen, microorganisms which are living, bacterial problem, fungi infected plant, nematodes, viruses affected problems in plants cannot be easily detect by human eyes. We should use some technology. With the help of machine learning technique we will process the images of the plants and try to predict plant disease.

Literature Review

The growth of a country depends on its business and also agriculture. Agriculture provides food and raw materials to the human and food industry. Food is essential need of human and plant diseases are big issue for farmers, it can be happened any time between sowing and harvesting. Plant disease does huge loss of crop and economy. Hence disease detection plays an important role in agriculture. Traditional method for leaf disease detection only is empty eye observation by human. Machine learning can be used for detecting diseases on plants. Machine learning is one of the sub parts of Artificial Intelligence to work automatically or give instructions to do a particular work. In machine learning we have to train the data and fit that trained data into models that it will result in useful information to the human. So we can use machine learning to detect diseases in plants. For the classification we can use colors of leaves, damaged amount of leaves, and area of the unhealthy plant leaf. For best accuracy we overviewed different machine learning algorithms to identifying different plant leaves diseases. Here, we take some of the papers related to Plant leaf diseases detection using various advanced techniques and some of them shown below,

Rakesh Kaundal et. al. [2006] authors concluded that support vector machine (SVM) based regression approach has led to a better description of the relationship between the environmental conditions and disease level. It could be useful for disease management. A comparison is done between the performance of conventional multiple regression, artificial neural network (back propagation neural network, generalized regression neural network) and support vector machine (SVM) [3]. Bashir Sabah et. al.[2012] authors proposed disease detection in Malus domestica by the method K-mean clustering, texture and color analysis. Here texture and color features used which are generally appear in affected areas; for the classification and recognition of different agriculture [8]. Sushma et.al. (2012) proposed that early detection if disease will help farmers do not use harmful chemicals on plants. In this research first to segregate images then detect pests process quality can be reduced by proposed algorithm [6]. Kulkarni Anand H. et. al.[2012] author describes a methodology for early and accurately detect plant diseases by using the combination of textures, color and features to recognize those diseases. Here the proposed approach is to use neural network (ANN) and diverse image processing techniques. The result of recognition rate is up to 91% [7]. DS Gaikwad et.al. (2016) author chooses pomegranate fruit for his examination, very colorful fruit. So using color problem empty eye can be detected. It is being affected very early because of its sweetness. Image processing in the disease detection methodology is used here [13].

Preetha et.al. (2016) proposed SVM algorithm for image processing, colors as an attribute in dataset. For classification of data photos author removed the morphological elements [15]. Fenghua Mei et. al. [2017] described a wheat disease automatic diagnosis system based on deep learning framework which is weekly supervised, i.e. deep multiple instance learning, which give result on plants image basis is detection of wheat diseases. Wheat Disease Database 2017 (WDD2017) is collected to verify the effectiveness of this system. The proposed system outperforms conventional CNN architectures on recognition accuracy under the same amount of parameters; it also specifies exact location for corresponding disease areas. The proposed system has been packed into a real time mobile app to provide support for agricultural disease diagnosis [22]. Andreas Kamilaris et. al.[2018], author discussed and perform a survey of 40 researches efforts that employ deep learning techniques, applied to various agricultural and food production challenges. To study the agricultural problems stated under each work, the specific models and frameworks employed the sources, nature and used dataset and overall performance achieved with help of used methods, comparison of deep learning with other techniques also done. It is stated that deep learning provides high accuracy by using image processing techniques [25].

Konstantinos P. Ferentinos et. al.[2018], author discussed about convolutional neural network models were developed to perform plant disease detection and diagnosis through deep learning methodologies using plants leaves images. Training of proposed models was done with the use of an open database of 87,848 images, containing 25 different plants in a set of 58 distinct classes of [plant, disease] combinations. Some models gets success 99.53% in detecting the corresponding combination [plant, disease]. High rate of success model is very usefull to early detection tool and also have possibilities of further expanded by researchers [26]. Budiarianto et.al. (2018) proposes Machine Learning techniques for recognition of disease in corn plant which is a main source of carbohydrate. CNN technique is used to improve plant disease. Researcher used different algorithms and use support vector machines (SVM), Decision Tree (DT), Random Forest (RF), and Naive Bayes (NB) to compare the results. By normal seeing of plant we can understand the problem like color difference. Different parameters are used for dataset attribute [30]. Shima et.al. (2018) proposed that plant disease cause decrease in food production. For detection purpose machine learning techniques are used by many researchers like RF processes, SVM processes, K-means processes, CNN processes. The random forest algorithm does the classification. The aim of author is to detect the disease with random forest classifier. We have to convert RGB type images to an HSV types images [27].

Prem et.al. (2018) proposed that some symptoms are visible from the eyes are wilting, spot, powdery mildew, galls, and dryness. Different attributes are taken in dataset, different techniques are used and different plots like box plot, bar plot are performed. With the help of statistical tests the prediction is done on inbuilt dataset. Many techniques are compared and the accuracy is different from each sample dataset [28]. Sherly et.al. (2019) proposed there are different type's bacteria or fungus is responsible for many different plant diseases. It can be predict using algorithm of Machine Learning. Many researchers try many algorithms and get differ results. The classification of diseases is hard to done by algorithms. By CNN technique we can identify the mulberry plant disease [31]. Balwant J Gorad et al.(2019)gives a better disease prediction system for brinjal plant. K-means clustering used to split the data that is provided by the farmers. Farmers collect images from their phone, tablet, camera and other sources that is forwarded to the system and then system create dataset from that and periodically it is done and hence plants diseases predicted by the system [35]. Monalisa Saha et al. (2020) takes the tomato and potato plants leaves to predict plant diseases. They collect both plant leaves images from internet sites and some images they collect with their digital camera from farming places. In proposed system after clustering if we give it (cluster) in multiple SVM classes then it gives better results and the performance analysis is 99% and the individual algorithm efficiency like k-means gives 88.6% and SVM gives 91%. Hence the proposed system is better than k-means and SVM [36].

Sridevi Sakhamuri et al. (2020) describe that there are three types of plant leaves diseases so they collect the leaves and maintain dataset according disease type. They collect different plants leaves like jasmine, grape, apple, beans, rose etc. and used different methods to detect leaves disease and get different accuracy like with k-means algorithm the accuracy was 88.8%, through SVM 95% accuracy was achieved and through ANN it was 70% to 95% for different

diseases [37]. Krishnaswamy Rangarajan et al. (2020) proposed an automated disease diagnostic system for ten diseases of four crops (eggplant, hyacinth beans, lime, lady finger). Author used six pre-trained deep learning models for training and validation of created dataset [38]. Pranesh Kulkarni et al. (2021) had taken public dataset for their research in which healthy and unhealthy images of apple, corn, grapes, potato and tomato plants were included. For the classification they used Random Forest Classifier. They got 93% accuracy through the system they developed [39]. Sahil Thakur et al.(2021) authors develop the model with CNN to identify the plant diseases with image processing. They used plants like potato, grape, corn, apple etc [40]. Gianni Fenu et al.(2021) review the researches from past 10 years in which different plants and crops were used like cherry, coffee, barley, grape etc. and used methods were SVM, SVR, KNN, ANN and many. Author observed that researchers need high quality labeled data for their research work [41].

Kow shik et al. (2021) used Convolutional Neural Network and Deep Neural Network to detect plant diseases. Author detect similar diseases from different plants like banana, beans, jackfruit, lemon, mango etc. The proposed method with CNN and DNN is feasible for early plant disease detection [42]. Jayashri et al. (2021) review the existing image processing techniques for disease prediction of pomegranate. They used SVM, ANN, KNN and PNN classifier to detect bacterial, fungal and viral diseases in fruit. K-means clustering for image segmentation, Fuzzy c means gives highest accuracy. According to them very few diseases were covered in the existing system [43]. Punithast al.(2021) reviewed many research papers on detection of plants disease using image processing techniques. For image processing they follow the procedure image acquisition, image pre-processing, image segmentation, feature extraction and disease classification. After comparison of many different models (which used SVM, ANN, KNN and other approaches on different plants) they found that SVM is most accurate method followed by ANN. [44]

CONCLUSION

Many research methods are there in deep learning to detect plant diseases in early stage. In existing methods SVM, ANN, CNN, KNN and other techniques are used. Effectiveness of each method may vary from one to another and it also depends on the dataset that how it is collected and trained. Plants used for research work are like tomato, potato, rice, beans, apple, pomegranate, maize etc. Plants disease detection research and applications is developing rapidly, still needed an application that works effectively for farmer of the nation of any region. Researchers should choose the crop or plant which is widely used for the human living like wheat, rice, potato etc. so that the productivity of that crop will be improved. Researchers should improve the quality of dataset they will use with the help of method of collecting data. We will take plants like we discuss earlier and will try to collect data (images) by self.

FUTURE DIRECTIONS

Although the plant disease identification model based on Machine Learning/deep learning review in this paper can overcome the complexity of the environment and improve the accuracy of identification, there are still some problems to be pointed out. For example, the algorithm needs repetitive iterative calculation and runs for a long time, which is not conducive to the fast identification results of this method. In future research, we will use the neural network to generate zero initial set corresponding to different leaves, which will increase the end of calculation limit for the iterative process of some algorithm, speed up the training speed, and end the iteration ahead of time.

As per the above stated study, the expected future of the research may be as follows:
(i) An improved plant disease prediction system will be introduced with the help of image, processing techniques.
(ii) The existing prediction models will be compared with the newly developed one. The comparison between these models will be analyzed on behalf of effectiveness.

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RESEARCH ARTICLE

The Groundwater Quality Analysis of Phaileng 'S' in Lunglei, Mizoram, India

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ABSTRACT

Many of the rural areas of Lunglei district depend on the groundwater for their secondary sources of water. The natural perennial springs which are seepages of the groundwater are vital for the inhabitants for domestic consumption, agriculture and other means of livelihood in Mizoram as they are the primary source of water in many areas. With the increase in population and the decline in quantity of the groundwater in recent years, the water that is consumed should be safe, clean, abundant and sufficient to maintain growth and development in the rural areas. Ensuring the quality by assessing the water sources is a must under BIS 10500:2012 standards. In this study, water samples from 10 natural springs from Phaileng 'S' village from Lunglei district in Mizoram were assessed for their physico-chemical and biological properties to determine their status for human consumption and other activities.

Keywords: Water quality, springs, groundwater, Lunglei, Mizoram.

INTRODUCTION

Everyone requires potable water, which is water that can be consumed by humans and animals. The availability of high-quality drinking water and securing its long-term supply to every household will be a priority for us all would have to take precautions. The demand for water has risen dramatically as the population has grown. In rural areas, In hilly areas like Lunglei, where subsurface water, groundwater, and precipitation are the primary sources of drinkable water, securing and maintaining their quality and sufficiency is a major problem for governments and people. It is extremely difficult to abolish and eliminate systems that impair water sources in rural communities,

where the need for water surpasses the processes and protections in place to protect local water sources. It's not just that enacting stronger laws isn't the best solution for the people; it's also that enacting stricter laws isn't always the best answer for the people. It is not only the government that is responsible for supplying safe drinking water in rural areas, but also the communities and every household. Phaileng 'S' is one of the villages within Lunglei Block of Lunglei district, Mizoram in North East India. Lunglei district is bordered by Bangladesh in the west and Myanmar to its east. This hilly village has a population of 308 as per the 2011 Census conducted by the Ministry of Home Affairs, Gov't of India. Phaileng 'S' village is located in the northern part of modern Lunglei town (Fig.1) covered under Toposheet No 84B/13 prepared by Survey of India and is located at 23°01'52" N and 92° 50' 49" E.

Phaileng 'S' and its adjoining areas are influenced by the SW monsoons, normally receiving heavy rains from May to September with little rains in the dry (cold) seasons. Like the other parts of Mizoram, the climate range from moist tropical to moist sub-tropical. Many of the inhabitants of this village receive domestic public water supply from the Public Health Engineering Department of the Govt of Mizoram which serve as the primary source of water. However, seepages of groundwater in the form of natural springs are crucial for the people as they serve secondary water sources in this agricultural dominated region. Fed by the monsoons, most of the springs of Phaileng 'S' are perennial with their quantity reduced in the cold months. Due to changing climate patterns groundwater seepages (spring water) scarcity has been common in other parts of Mizoram in recent years [1] and [2]. Thus groundwater water resources in the form of springs are becoming ever more important as the population keeps on increasing. The lithology of the study area is dominated by sandstones, shales, siltstones of Middle Bhuban formation of the Surma group. Many workers have studied the quality of groundwater from India and North East India [3-9]. Studying and assessing the quality of groundwater is necessary as it is directly linked with the health and progress of any society. Sources of biological pollutants in drinking water. Unsanitary and filthy conditions are still common and pervasive in India's rural communities today. Now, though, with the deployment of new government schemes and programmes to address the difficulties of sanitary conditions for minimising water-borne infections such as typhoid, diarrhoea, and other diseases, such as in the last few years, the number of cases of waterborne infections has decreased dramatically. The results in Mizoram imply that Public Health Engineering Department which is the government agency for providing water in urban area is better than tuikhurs (subsurface water); however, the quality of water from both sources, which is used for drinking and domestic purposes, was determined to be more or less within the tolerance levels. But in most rural places, groundwater quality was also found to be safe for human consumption.

MATERIALS AND METHODS

A total of 10 natural springs within Phaileng 'S' village were selected for the study. In-situ assessment of the water samples for pH were done using *Apera AI311*, *Hofun* portable tester was used for testing both TDS and E Conductivity values of the water sources and the total hardness of the water sources were assessed using *Accu Plus Portable* tester. For the other parameters, water samples of 1 L each were collected using *Tarson* bottles using the grab sampling method as per the methods of [10] in the month of July, 2021. All the bottles were capped and sealed tightly to avoid any leakage which could happen during transportation and the sample bottles were placed *in PSM Vaccine Carrier* Ice boxes. The water samples were then analysed at the Mizoram State Referral Institute, Govt of Mizoram (NABL Accredited Laboratory), Aizawl using BIS 10500:2012 standards Table.1.

RESULTS AND DISCUSSION

The pH of all the water samples collected from Phaileng 'S' are within the permissible limits as prescribed by BIS 10500:2012. This pH determines how acidic or basic the water is. Five water samples > 7 pH indicate basic water sources and the other 5 water samples show acidic water amongst the water sources in their permissible limits. The reason for their acidic nature could be due to burning of forest cover (jhumming) practises, which when they reached the groundwater after water percolates in the groundwater, they tend to change the pH of water. The Turbidity of

water indicates the presence of sediments suspended in the water, and all the water sources are having 1 NTU values which are all within the desired limit for potable water. The physical parameter of E conductivity which measures the amount of dissolved substances show that all the water sources have very less amount of impurities and they all have values < 187 µ/mhos/cm. The Total Dissolved Solids (TDS) could be organic, inorganic compounds or concentration of any dissolved particle. The permissible limit of TDS is 500 mg/l and all the water samples show TDS values < 78.0 mg/l. The alkalinity is an important chemical parameter for the water sources which is their capacity to neutralize the acid present in water. All the water samples have Alkalinity values between 10.0-28.0 mg/l which are all under the permissible limits as per BIS 10500:2012 standards and the reason for their low values can be attributed to the fact that the study area is a rural area, so activities like urbanization like cement and construction materials which can increase the alkalinity values don't reach the groundwater and hence they are very low. The total hardness values of the water samples are all well within the permissible limits. Since hardness of water could also be defined by the presence of carbonate terrain and its local geology, there are no rocks which could influence the hardness values since all the rocks are of arenaceous and argillaceous rocks, and this is why none of the samples have total hardness values < 32.0 mg/l. Fluoride upto 1 mg/l is permissible in potable water in BIS 20100:2012 standards. Excessive exposure to fluoride > 1 mg/l in consumed water leads to dental and skeletal fluorosis. Frequent exposure to Iron (Fe^{2+}) in potable water can promote bacteriological growth and increase the turbidity of water. The troublesome chemicals like Iron (Fe) and Flouride (F) are totally absent in all the water samples. Faecal coliform gives information on the presence of sewage wastes, pollutants and other bacteriological pollutants is an unhealthy indicator in water sources. All the water sources also have no indication any biological constituents which are reflected by the absence of Faecal coliform.

CONCLUSION

rom the assessment of all the physical-chemical parameters of water samples from the different natural springs in Phaileng 'S' it has been found that all the water sources are well within the permissible limits of BIS 10500:2012 standards and can be consumed for domestic, agricultural, development and other purposes. It is recommended that every household must have provisions for rainwater harvesting which is the purest form of water. Also more public water storage tanks must be built for the dry seasons. To prevent any bacteriological contamination of the water sources strict guidelines and laws must be adopted and enforced for judicial and sustainable use of water sources in the village.

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Table 1: Results of Physico-Chemical and Bacteriological parameters of water samples analysed

Sample No	pH	Turbidity NTU	EConductivity µ/mhos/cm @ 25.5°c	TDS mg/l	Alkalinity mg/l	Cl mg/l	Total Hardness mg/l	Fe mg/l	F mg/l	Faecal Coliform (cfu)
1	6.4	1.0	110.9	65.8	26.0	10.0	16.0	NIL	NIL	NIL
2	7.4	1.0	91.7	78.0	24.0	8.0	28.0	NIL	NIL	NIL
3	7.5	1.0	87.3	77.0	24.0	6.0	28.0	NIL	NIL	NIL
4	7.5	1.0	91.8	74.0	28.0	10.0	30.0	NIL	NIL	NIL
5	7.6	1.0	102.2	77.0	24.0	6.0	28.0	NIL	NIL	NIL
6	6.8	1.0	135.3	49.7	20.0	16.0	26.0	NIL	NIL	NIL
7	5.8	1.0	187.0	24.4	14.0	14.0	32.0	NIL	NIL	NIL
8	6.6	1.0	74.9	22.0	14.0	12.0	28.0	NIL	NIL	NIL
9	7.6	1.0	114.0	76.0	24.0	8.0	28.0	NIL	NIL	NIL
10	6.9	1.0	101.3	38.6	10.0	17.0	32.0	NIL	NIL	NIL

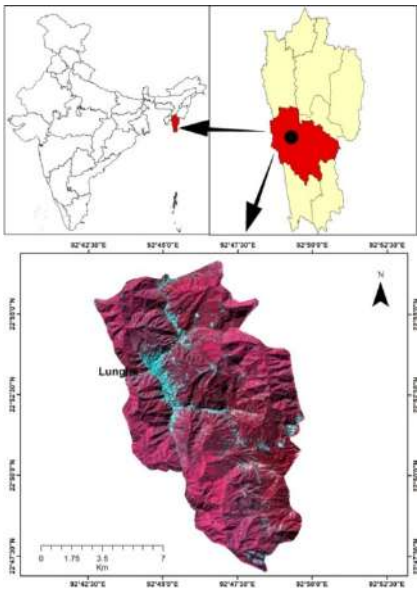

Fig 1: Location of the study area

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RESEARCH ARTICLE

Formulation of Nanogel Containing Garlic Extract for Treatment of Acne

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ABSTRACT

The aim of present work was formulation and evaluation of topical nanogel containing garlic extract. The topical nanogels of garlic extract were formulated for the treatment of acne. The preparation of garlic powder was done by temperature controlled extraction process and powder obtained was light yellowish colour. The identification of drug was done by using Thin Layer Chromatography. Nanogels of garlic extract were formulated in water as a vehicle after evaporation of methanol. The drug-excipient compatibility study using FT-IR spectra of drug, empty nanogel and final formulation was done and from these spectra, it was concluded that the peaks of drug were remained intact indicating no chemical interaction occurs between the ingredients. The nanogels of garlic extract were formulated by emulsion/solvent evaporation method using Pluronic F127 and Polyethyleneimine polymer. The anti-microbial study of was done by using agar well diffusion method using one of the acne inducing bacteria *Propioni bacterium acnes*. The result obtained in the present study suggests that Nanogel containing garlic extract has significant scope to develop a unique broad spectrum of anti-acne herbal nanogel.

Keywords: Topical formulations, Propionibacterium acnes, Nanogel, Pluronic F127.

INTRODUCTION

Acne vulgaris is a common inflammatory disorder of the sebaceous glands characterized by the presence of blackheads with papules, pustules and in more severe cases – cysts and scars. Although the actual cause is still

unknown, many physicians believe acne is an infection. In particular *Propionibacterium acnes* and *Staphylococcus epidermidis* [1,2] can infect tiny oil-secreting sebaceous glands found in large numbers on the face, upper back and chest and they will accumulate and produce a secondary infection. This leads to a worsening of clinical symptoms, making acne extremely difficult to treat. Unfortunately, many antibiotic treatments are unable to kill off *Propionibacterium acnes* and *Staphylococcus epidermidis* infection, since the bacteria are drug resistant [3, 4]. Garlic possesses a defence mechanism against attack from the soil-borne organisms. It has been found that invasion of growing garlic cloves by fungi and other soil pathogens causes the alliin and allinase to react, rapidly producing localized bursts of allicin which deactivates the invaders. This ability underlies the exceptional capacity of allicin to kill unwanted organisms [3].

Among most of the topical formulations, Nanogels can deliver the active moiety in controlled and sustained manner. Release of therapeutics can be regulated by crosslinking densities. Crude garlic extract cannot be applied directly on skin due to its irritant nature & may sometimes produce burns on the applied area. Therefore slow delivery of the extract can reduce the irritation & prolong the therapeutic action of garlic extract. Being cross-linked structure, nanogels are not easily washed off the applied site, which also helps in maintaining the prolonged action of therapy. Formed nanogel containing garlic extract was tested for the activity against Propionibacterium acnes for its antiacne activity.

MATERIALS AND METHODS

PREPARATION OF GARLIC POWDER

Garlic used for the extraction of garlic powder was purchased from the local market. Rest of the materials for synthesis of nanogels, and characterization, analysis, etc. were purchased from different vendors. Preparation of garlic powder was done by temperature controlled extraction process as described by British Pharmacopoeia (2009) [5] and from the book 'Allicin – The Heart of Garlic' by Peter Josling [6].

DETERMINATION OF ALLICIN CONCENTRATION IN GARLIC POWDER

High performance liquid chromatography (HPLC) was used for determination of allicin concentration in garlic powder, according to the method given in British Pharmacopoeia (2009) [5].

PREPARATION OF DRUG-LOADED F127/PEI NANOGEL

Preparation of drug-loaded Pluronic F127/PEI nanogel was done as per the method given by Li et al. (2011) [8].

Preparation of CDI-activated Pluronic F127

A solution of Pluronic F127 (1.25 g, 0.1 mmol) in anhydrous THF (15 mL) was added drop-wise (during 2 hr.) to an excess amount of CDI (0.81 g, 5 mmol) in THF (15 mL) at room temperature under nitrogen atmosphere. After the addition, the mixture was kept stirring for an additional 6 hr. The solution was concentrated to a small volume under vacuum and poured into ethyl ether (150 mL), and the precipitate was collected by filtration to get CDI-activated Pluronic F127. This process was repeated three times to remove the unreacted CDI. The CDI-activated Pluronic F127 was obtained as white powder after drying under vacuum at room temperature for 12 hr.

Preparation of F127/PEI nanogel

The F127/PEI nanogel was prepared by an emulsification/solvent evaporation method. The activated Pluronic F127 was dissolved in chloroform and added drop- wise to an aqueous solution of PEI under stirring. The mixture was sonicated for 3min and the organic solvent in the emulsion was removed by rotary vacuum evaporation at 50°C for 45 min. The remaining solution was centrifuged at 3000 rpm for 30 min to remove adhesive fragments. After neutralizing with hydrochloric acid, the solution was dialyzed in a dialysis bag with 14,000 – 16,000 Da molecular weight cut-off against water at pH 4.0. The purified nanogel samples were freeze dried to obtain F127/PEI nanogel.

Drug loading

The drug and lyophilized empty nanogels were dissolved separately in mixture of methanol and water (1:1), and then both were mixed and the solvent was subsequently removed by rotary vacuum evaporation. The resulting film formed was further hydrated with a suitable amount of phosphate buffered saline pH 7.4.

SCREENING STUDIES OF PROCESS VARIABLES

The effects of following independent variables were studied by trial & error method (Table 1).

A. Concentration of Pluronic F127 (mg)

B. Concentration of Polyethylenimine (PEI) (mg)

The effects on the following dependent variables by the change in independent variable were studied by trial and error method and the results of screening study were shown in Table 1

A. Particle size (nm)

B. Entrapment efficiency (%)

C. Cumulative drug release (%)

OPTIMIZATION

For the present work, factorial design was applied to obtain optimized formulation. The optimization was done by using Design Expert software (v8.0.7.1)

3^2 FULL FACTORIAL DESIGN

In this experiment, the concentration of Pluronic F127 and concentration of PEI may have impact on the quality of nanogel and hence were selected as independent variables. In this design (Table 2), two factors were evaluated each at three level in such a way that low level was -1, medium level 0 and high level +1 (table 2).

Evaluation for optimization

Particle size

The droplet size of the nanogel loaded with garlic powder was measured by using Malvern zeta sizer according to the method described by Singka *et al*. (2010) [10]. The nanogel (1-1.5 ml) was transferred to a disposable polystyrene cuvette and the droplet size of the nanogel was determined at an angle of 90° at 25°C.

Drug entrapment efficiency

Measurement of drug entrapped into the prepared nanogel was done by the method described by Azadi *et al*. (2012) [12]. To determine drug loaded amout, the nanogels were centrifuged at 12,000 rpm for 10 min. The supernatant was analyzed by HPLC after suitable dilution and 20 µl injected. The % entrapment efficiency of drug in nanogels was calculated

***In-vitro* release study**

In vitro drug release study of prepared nanogels was performed according to the method given by Azadi et *al*. (2012) [12] using Franz diffusion cell and dialysis membrane 50. The receptor compartment was filled with 25 ml of phosphate buffered saline pH 7.4 diffusion media. The donor compartment was placed in such a way that it just touches the diffusion medium in receptor compartment. The 5 ml nanogel was placed in the donor compartment. The whole assembly was fixed on magnetic stirrer and the solution in the receptor compartment was continuously stirred using magnetic beads to ensure uniform distribution of permeating solutes for later sampling and the vessels were double-jacketed with water circulating between the jacket walls throughout the study to maintain the temperature 37 ± 0.5°C. 2 ml sample of the receptor fluid were withdrawn at predetermined time intervals and replaced immediately with same volume of fresh diffusion media. The samples were analysed for drug diffused from the membrane at 254 nm using HPLC.

EVALUATION OF OPTIMIZED NANOGEL

pH

The pH of nanogel formulation was determined using digital pH meter as per the method described in Indian Pharmacopoeia (2007) [9].

Viscosity

The viscosity of the prepared formulations was determined using Brookfield viscometer as the method described by shah *et al*. (2012) [13]. The viscosity measurements were made in triplicate.

Particle size

The particle size of the optimized nanogel was measured as per the method described above.

Drug entrapment efficiency

Drug entrapment efficiency of optimized nanogel was measured as per the method described previously.

In-vitro release study

In vitro drug release study of optimized nanogel was performed as per the method described previously.

Ex-vivo skin permeation study

The skin permeation study was performed by using rat skin as per the method given by Singka *et al*. (2010) [15]. The diffusion area of franz diffusion cell was 1.51 cm^2 and had a receptor volume of 25 ml. The procedure of this study was same as per *in-vitro* diffusion study as described above except that, instead of dialysis membrane the rat skin was mounted on franz diffusion cell.

Anti-acne study

An agar well diffusion method was used for determination of antibacterial activity of optimized formulation against one of the acne inducing bacteria *Propionibacterium acnes* according to the Sukatta *et al*. (2008) [15]. Bacteria were suspended in sterile nutrient broth medium and incubated for 24hr. The suspension (100µl) was spread on surface of nutrient agar in petri-dish. Wells were cut from the agar with sterile cork borer and formulation was delivered into them. The inoculated plates of *Propionibacterium acnes* were incubated anaerobically at 37°C for 24hr. Antibacterial activity was evaluated by measuring the diameter of inhibition zone of tested bacteria.

Stability study

The stability study of optimized formulation was performed as per the ICH guideline Q 1 $C^{81.}$. The optimized formulation was kept for stability study at 40 ± 2°C / 75% ±5% RH (relative humidity) and for freezing condition at 4 ± 0.05°C as per ICH guideline for 1 month. After one month, the sample was observed for any change in globule size and % entrapment efficiency.

PREPARATION OF DRUG-LOADED F127/PEI NANOGEL

Dose calculation

Marketed formulation contains 180 mg of allicin. So, from the calculation it was found that 3.82 g of garlic powder used can provide 180 mg of allicin. The F127/PEI nanogel was prepared by an emulsification/solvent evaporation method using different proportion of polymers as described by Li *et al*. (2011) [8]. The activated Pluronic F127 were dissolved in chloroform and added drop-wise to an aqueous solution of PEI under stirring. After neutralizing with hydrochloric acid empty nanogel samples were freeze dried. Then drug and lyophilized empty nanogels were dissolved separately in mixture of methanol and water, mixed it and the organic solvent was subsequently removed by rotary vacuum evaporation. The resulting film formed was further hydrated with a suitable amount of phosphate buffered saline pH 7.4 to obtain yellowish liquid nanogel formulation.

RESULTS OF PRELIMINARY SCREENING

Effect of polymer concentration

Preliminary screening was done by measuring effect of concentration of Pluronic F127 and concentration of Polyethylenimine (PEI) on particle size and poly dispersity index (PDI) (Table 4). In preliminary batches, high concentration of Pluronic F127 as compared to concentration of PEI gave small particles of nanogel. Concentration Pluronic F127 gave small size nanogel up to the certain concentration and afterward increases the particle size. The ratio of concentration of Pluronic and PEI as 1:1 gave acceptable particles of nanogel then higher and lesser ratio.

Effect of stirring rate

There is no significant effect of stirring was observed on particle size of nanogel formulation (Table 5). At low and higher speed of stirring, nearly same particle size of nanogel was observed.

OPTIMIZATION OF FORMULATION

On the basis of preliminary screening study, the following variables were selected.

Independent variables

1.Concentration of Pluronic F127 (X_1) and

2.Concentration of PEI (X_2)

Dependent variables

1. Particle size (Y_1)
2. % entrapment efficiency (Y_2)
3. % cummulative drug release (% CDR) (Y_3)

3^2 FULL FACTORIAL DESIGN

A 3 level 2 factors factorial design (3^2) was employed to design sustained release nanogel formulation of garlic powder. The design was employed to study the effect of independent variables, i.e. concentration of Pluronic F127 (X_1) and concentration of PEI (X_2) on dependent variables particle size (Y_1), % entrapment efficiency (Y_2) and % CDR (cummulative percentage Drug Release) (Y_3) (Fig 1) (Table 6).

Effect on % cumulative drug release

From the drug release of F1 to F9 formulations, it was found that all the formulation gave initial burst release of drug in first half hours and afterward provides sustained release of drug from the formulation up to 10 hrs. All the formulation were shown release of more than 80 % of drug in 10 hr. and more than 90 % of drug in 12 hr. (Table 7) (Fig. 1).

CHARACTERIZATION OF OPTIMIZED NANOGEL FORMULATION (F2).

pH

The pH of optimized nanogel was determined using digital pH meter. The optimized formulation of nanogel had pH 5.51 ± 0.0152, which is similar to the pH of skin i.e., 4 – 7.

Viscosity

The viscosity of optimized nanogel was determined using Brookfield viscometer. Using spindle no S63 at 100 rpm, the viscosity of optimized nanogel formulation was found to be 2.68 ± 0.13. As the concentration of polymer solution increases viscosity also increases.

Particle size

The particle size of optimized nanogel was measured by using Malvern zeta sizer. Particle size of optimized nanogel was found to be 81.97nm which is desired for the nanogel

Drug entrapment efficiency

Drug loaded amout of optimized nanogels was measured by HPLC after centrifugation at 12,000 rpm for 10 min. The % entrapped drug in optimized nanogel was found to be 76.67 %.

***Ex-vivo* skin permeation study**

The skin permeation study was performed by using rat skin. Samples were withdrawn and analysed for drug diffused through the skin at 254 nm using HPLC. From skin permeation study using rat skin it was found that the optimized formulation of nanogel can pass through the skin and had a 90.58 % of drug release showing sustained manner (Fig. 2) in 12 hrs. (Table 8).

***In-vitro* Drug Release profile**

In-vitro drug release study of optimized nanogel was performed using franz diffusion cell. From the release study, it was found that optimized nanogel shows initial burst release of drug in first half hours and afterward provides sustained release of drug (Fig. 3). The optimized nanogel was shown release of more than 90 % (96.42 %) of drug in 12 hr. (Table 15)

Anti-acne study

An agar well diffusion method was used for determination of antibacterial activity of optimized formulation against one of the acne inducing bacteria *Propionibacterium acnes*. The three samples, distilled water (control), garlic powder solution (standard) and garlic containing nanogel formulation (test) were used for this study (Fig. 4). Anti-microbial study of optimized nanogel formulation and solution of garlic powder having 2 mm and 3 mm of zone of inhibition, respectively. So, from the result of anti-microbial study it should be concluded that optimized nanogel formulation having inhibitory effect on one of the acne inducing bacteria *Propionibacterium acnes*

Stability study of the optimized nanogel was performed as per ICH guideline. After 1 month of stability study formulation was evaluated for its particle size and % entrapment efficiency. From the results it was found that formulation was shown increase in particle size and decrease in % Entrapment efficiency at refrigeration condition (4 ±0.05 °C) (Table 9). While formulation stored at 40 ± 2°C/75% ± 5% RH (relative humidity) was being precipitated and degraded. So, it was concluded that optimized nanogel formulation was stable at refrigeration condition and unstable at room temperature [18].

CONCLUSIONS

In conclusion, this research suggests that *garlic extract* have potential against acne causing bacteria and hence they can be used in topical anti-acne preparations and may address the antibiotic resistance of the bacteria. The optimized nanogel formulation of garlic extract seems to be a sustained and controlled release dosage form. The pH of optimized formulation was suitable for the skin and can be applied topically. Anti-microbial study was shown that garlic extract nanogel having good inhibitory effect on acne inducing bacteria *Propionibacterium acnes*. The skin irritation study was shown that the nanogel of garlic extract having no irritant effect of garlic after incorporation in the nanogel formulation. The stability study of optimized formulation was shown that the nanogel having good stability at refrigeration condition but unstable at room temperature. Further research on the bioactivity of optimized nanogel containing garlic extract is planned in future work as there is a need for new therapeutics for *P. acnes*

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Table 1: Optimization of polymer concentration

Sr. no.	Concentration of Pluronic F127 ( )	Concentration of PEI ( )	Ratio of PF127/PEI
1	200	50	4:1
2	300	100	3:1
3	200	100	2:1
4	100	100	1:1
5	100	200	1:2
6	100	300	1:3

Table 2: 3^2 Factorial Design Layout

Batch	Coded value	Actual values	Coded values	Actual values
	X_1	Pluronic F127 (mg)	X_2	PEI (mg)
F1	-1	100	-1	100
F2	0	200	-1	100
F3	+1	300	-1	100
F4	-1	100	0	200
F5	0	200	0	200
F6	+1	300	0	200
F7	-1	100	+1	300
F8	0	200	+1	300
F9	+1	300	+1	300

Table No 3: Formulation Table

Batch	Drug (g)	Concentration of Pluronic F127 (mg)	Concentration of PEI (mg)	Water (ml)	Chlorofor m (ml)
F1	3.82	100	100	20	2
F2	3.82	200	100	20	2
F3	3.82	300	100	20	2
F4	3.82	100	200	20	2
F5	3.82	200	200	20	2
F6	3.82	300	200	20	2
F7	3.82	100	300	20	2
F8	3.82	200	300	20	2
F9	3.82	300	300	20	2

Table no 4: Effect of polymer concentration on particle size

Sr. no.	Concentration of Pluronic F127 (mg)	Concentration of PEI (mg)	Ratio of PF127/PEI	Particle size (nm)	PDI
1	200	50	4:1	166	1
2	**300**	**100**	**3:1**	**32.68**	**0.691**
3	200	100	2:1	49.39	0.777
4	100	100	1:1	141.5	0.461
5	100	200	1:2	755	0.258

Table: 5 screening of stirring rate

Batch code	Stirring rate (rpm)	Particle size(nm)
A1	1000	49.39
A2	2000	48.75
A3	3000	48.26

Table 6: 3^2 Full factorial design

Sr. No.	Batch Code	Actual Value		Responses		
		Factor 1 conc of Pluronic F127 (mg) (X_1)	Factor 2 conc of PEI (mg) (X_2)	Particle Size (Y_1) (nm)	% Entrapment Efficiency (Y_2) (%)	% cummulative drug release (Y_3) (%) (12 hr.)
1	F1	100	100	131.8	70.83	95.58
2	F2	200	100	81.97	76.67	96.42
3	F3	300	100	56.18	46.38	95.84
4	F4	100	200	714.6	48.81	93.28
5	F5	200	200	711.6	67.78	94.68
6	F6	300	200	520.2	46.15	94.06
7	F7	100	300	331.3	45.07	93.24
8	F8	200	300	290.4	68.42	95.21
9	F9	300	300	144.1	58.4	95.73

Table: 7 *In-vitro* drug release profile of nanogel formulations of batches F1- F9

	% CDR								
Time (hr.)	0.5	1	2	3	4	6	8	10	12
F1	12.04	27.06	52.05	61.97	69.22	80.21	89.04	93.01	95.58
F2	10.54	16.13	24.1	32.19	39.19	53.53	68.17	82.4	96.42
F3	12.45	19.24	28.44	37.47	45.22	58.81	72.84	85.46	95.84
F4	13.38	25.5	38.08	47.77	55.69	65.52	76.41	85.25	93.28
F5	14.26	29.31	55.76	65.63	70.34	81.39	90.71	92.78	94.68
F6	10.56	22.16	34.65	42.58	49.74	60.82	73.2	84.5	94.06
F7	11.44	28.33	48.22	58.33	65.89	74.03	83.76	88.4	93.61
F8	12.26	27.75	46.01	56.15	60.95	69.54	78.49	85.3	95.21
F9	11.32	26.76	53.85	61.32	68.21	78.25	88.55	93.67	95.73

Table: 8 *Ex-vivo* skin permeation profile of optimized nanogel formulation

Time (hr.)	0.5	1	2	3	4	6	8	10	12
%CDR	7.03	13.12	21.66	29.02	35.63	47.18	61.03	75.97	90.58

Table 9: Data of Stability study of optimized batch F2 at 4 ± 0.05°C

Parameter	Time	Before stability	After stability
Particle size	1 month	81.97	96.23
% Entrapment efficiency	1 month	76.67 %	72.44 %

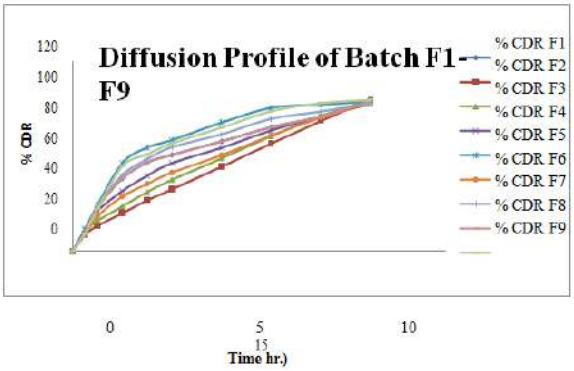

Figure: 1 Comparative *In-vitro* drug release profile of nanogel formulations of batches F1-F9

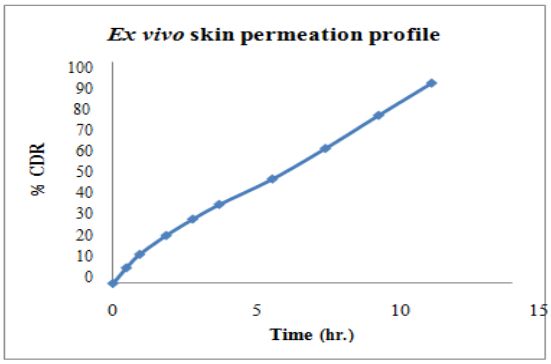

Figure: 2 *Ex-vivo* skin permeation profile of optimized nanogel formulation

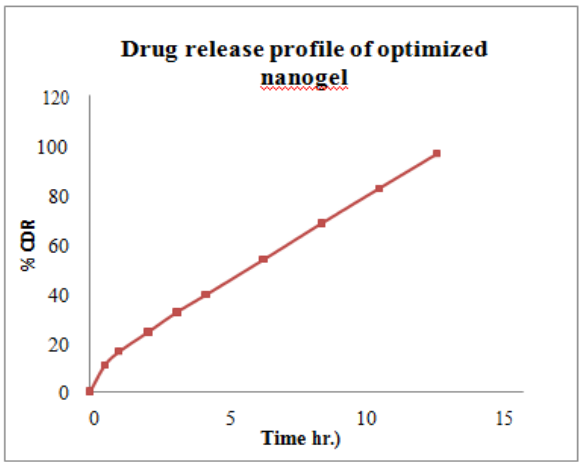

Figure 3: Drug release profile of optimized nanogel

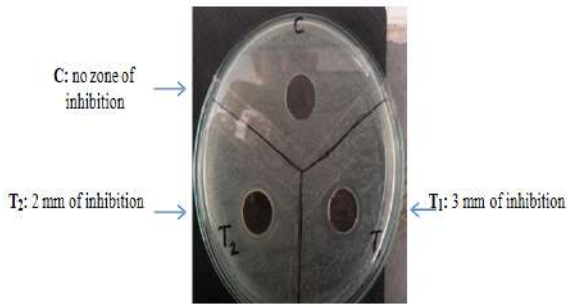

Figure 4: Zone of inhibition of control (C), solution of garlic extract (T_1) and optimized nanogel (T_3)

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RESEARCH ARTICLE

Block Chain and the Internet of Things in Healthcare Applications

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ABSTRACT

Healthcare is that the most prominent field suitable for the applications of machine learning and massive data on health care data. The implementations of health care with big data and machine learning is increased with the client health requirements. The electronic health record applications are being increased during this current situation, which is required to be focused on utilizing the information generated by those applications. there's an oversized volume of information in health care that's associated with different health care domains especially neuro and cardiac. These data need a special focus and therefore the architectures currently that specialize in these domains needs to implement the most recent technologies to predict some patterns. during this article, the implementation of various health care architecture is focussed, which uses live data gathered from different sources over the world. during this article, machine learning approaches and therefore the big data framework are combined to style a prediction model and data handling techniques

Keywords: Administration, Healthcare, Machine learning, Artificial intelligence, Block Chain.

INTRODUCTION

Artificial intelligence is becoming increasingly useful for doctors, nurses, radiologists, researchers, pharmacists, emergency medical service, and plenty of other healthcare professionals. This paper proposes the creation of a wise healthcare system using computer science as a way of efficiently solving challenges within the healthcare industry and as a tool for optimizing patient care plans. The proposed AI-assisted system shows that it can support a patient who is admitted to the hospital through emergency medical services, easily process the patient's data, and offer early detection of significant diseases. It can automatically recognize the complicated patterns which are obtained from

radiologists, can analyze complete human molecular data and genetics within the clinic, and might support doctors by producing AI-generated radiologist reports, clinical laboratory reports, and plenty of other decision-support tools. The proposed architecture can easily handle diverse and sophisticated Healthcare problems and may be utilized by any modern hospital to avoid wasting time and money. This Work also shows the recent development of AI applications in healthcare, which can be utilized in the proposed architecture.

Literature Survey

Internet of Things (IoT) could be a revolutionary communication paradigm which plays a necessary role within the field of remote monitoring and control operations. This paper proposed the overview of IoT based remote monitoring and control systems which potentially solve societal issues within the field of healthcare, environment, home automation, transportation, military, agriculture, solid waste management, smart metering, surveillance, consumer asset tracking, smart grid, vehicular communication system and pilgrims monitoring. Internet of Things (IoT) plays a significant role within the field of healthcare. The event of smart sensors, smart devices, advanced lightweight communication protocols made the likelihood of interconnecting medical things to watch biomedical signals and diagnose the diseases of patients without human intervention and termed as Internet of Medical Things (IoMT). This paper portrays an summary of Internet of Medical Things based remote healthcare, tracking ingestible sensors, mobile health, smart hospitals, enhanced chronic Disease treatment.

PROPOSED METHODOLOGY

The Internet of Intelligent Things (IoIT) communication environment is utilized in various kinds of applications (for example, intelligent battle fields, smart healthcare systems, the commercial internet, home automation, and plenty of more). Communications that happen in such environments can have differing types of security and privacy issues, which might be resolved through the employment of blockchain. During this paper, we propose a tutorial that aims in designing a generalized blockchain-based secure authentication key management scheme for the IoIT environment. Moreover, some issues with using blockchain for a communication environment are discussed as future research directions. the small print of various kinds of blockchain also are provided. a number of the widely-accepted consensus algorithms are then discussed. Next, we discuss differing kinds of applications in blockchain-based IoIT communication environments. The small print of the associated system models are provided, such as, the network and attack models for the blockchain-based IoIT communication environment, which are helpful in designing a security protocol for such an environment. A practical demonstration of the proposed generalized scheme is provided so as to live the impact of the scheme on the performance of the essential parameters. Finally, a number of the long run research challenges within the blockchain-based IoIT communication environment are highlighted, which can even be helpful to the researchers.

Future Work

Treatment as of both regular and emergency can be provided through Cloud-based services to the patient's located in remote areas. The use of 5G mobile communication technologies has increased the servicing of healthcare provider to remote patients with the help of Internet of things connected with sensors for monitoring blood sugar level, ECG (Electrocardiogram), thyroid level, blood pressure, cholesterol level. Larger volume of data is processed through internet with minimum delay at regular intervals regarding the critical patients in remote or in urban. Hence centralization of health monitoring for various people at variety of places is quite possible.

CONCLUSION

Internet of things has made tremendous jobs in the healthcare industries that have faced with several issues in regulating treating methods and provision of treatment advices to patient either in critical care or regular. Deep learning techniques have made a remarkable imprint in identifying the patient condition and treatment application. Advancement in the technology has increased the life time of each person by identifying and treating health activities.

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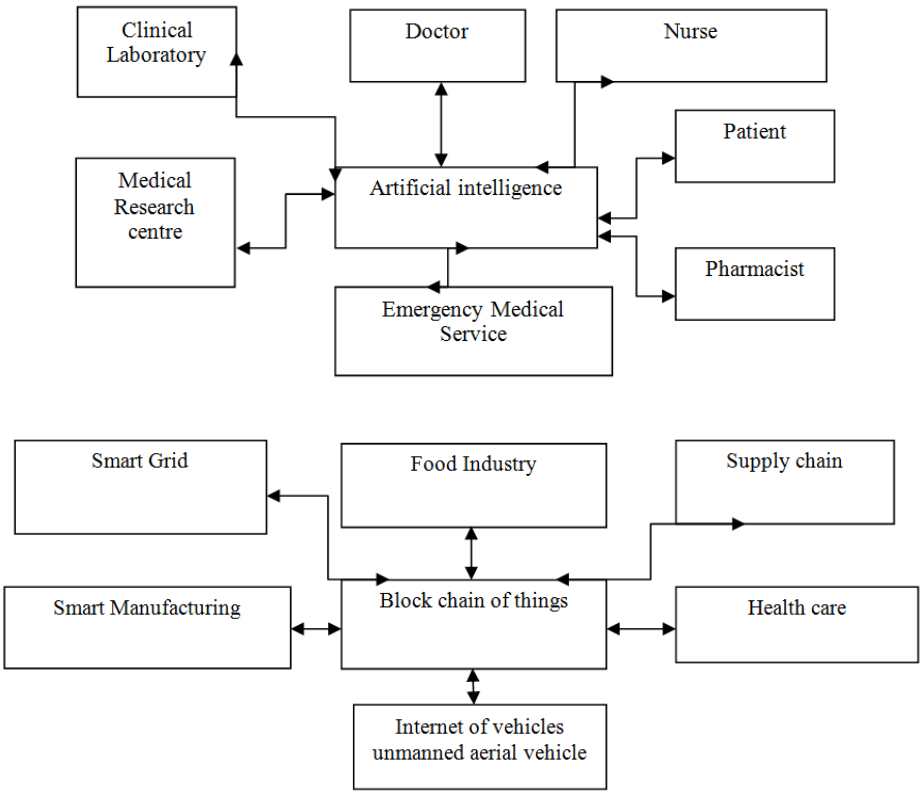

Fig 1 Block chain-based IoIT communication environment

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RESEARCH ARTICLE

Mean Time to System Failure Analysis of a Standby System with Delayed Rectification and Random Switch

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ABSTRACT

A good server and a reliable switch are main requirements for the smooth functioning of a standby system. In this paper, a probabilistic model is developed for a cold standby system with the possibility of standby failure, a random switch and arrival time of the server. The system analysis is done using semi-Markov process and regenerative point technique. In order to show the practical importance of theoretical results drawn and for the wider applicability of the model, particular cases are discussed for Weibull distribution with fixed shape parameters and different scale parameters and results are concluded in tabular form.

Mathematics Subject Classification 2020: 60K20

Keywords: Random switch, Arrival time, Semi-Markov process, Regenerative point technique, Weibull distribution.

INTRODUCTION

The cold standby is a common redundancy technique which is widely used because of its proven results in improving system reliability and availability. There is extensive literature concerning the standby systems. Many of the researchers have studied standby systems by incorporating various concepts (Gupta and Goel, 1989; Goel et al., 1995; Bhardwaj and Malik, 2010; Jia et al., 2016). A cold standby system generally assumes that the standby unit never fails in the standby mode but the possibility of its failure is realistic due to impact of various environmental factors like rust, excess moisture etc. or may be some other factors such as lack of oiling, proper maintenance etc. This genuine cause was initially underlined by (Osaki and Nakagawa,1971). Later on, Bhardwaj et al., 2017, carried out research work on cold standby failure with non-instantaneous replacement of a failed component. It is evident that to yield desirable results from a cold standby redundancy technique, importance should be given to how swiftly a standby unit is turned on for operation. This is possible only if we have a reliable switch and a quick server which is expected to do his task swiftly to avoid any hassle in the smooth functioning of the system. If a server is not present in the system at the time of need, then system rectification is not possible. The issue concerning delayed

repair is discussed by Bhardwaj and Singh, 2015.Further, Kuo and Ke, 2016 compared the availability of three repairable systems with the unreliable server.

The wider applicability of Weibull distribution to handle various failure modes is the reason to do system analysis using this distribution. A connected study is presented by Gupta et al., 2013 but needs further exploration under the view of mixed parametric assumptions. From the above discussion it is clear that a cold standby system with reliable switching devices accompanied by a quick server are central elements to keep a system running smoothly for a desired time. The server plays an important role for the long-run reliability of a system as he is responsible for restoring a system to an operative state again. But sometimes the server is not available with the system all the time because of his preoccupation in some other high priority tasks. This leads to a delay in his arrival which eventually leads to an increase in downtime of the system. This may lead to serious concerns. To by-pass these consequences we have combined cold standby failure and switch failure which undergoes rectification after failure along with arrival time of server and tried to model a system which would give us high MTSF and hence the reliability. In this study, the system starts with two identical units. The working unit after failure goes for immediate repair. The standby is taken for inspection for repair/replacement. The function of switch is to turn the standby on after failure of working unit. At this time it may or may not be functional. The server takes some time to initiate rectification task. The system analysis is done using semi-Markov process and regenerative point technique. In order to show the practical importance of theoretical results drawn and for the wider applicability of the model, particular cases are discussed for Weibull distribution with fixed shape parameters and different scale parameters and results are concluded in tabular form.

States of System

The following are possible transition states of the system model:

Regenerative states

$S_0=(O,CS), S_1=(F_{wr},O), S_2=(F_{wr},CS_{nso},S_{wr}), S_3=(O,F_{wi}), S_4=(F_{ur},O), S_5=(O,F_{ui})$

Non-Regenerative states

$S_6=(F_{WR},CS_{NSO},S_{ur}), S_7=(F_{WR},F_{wi},S_{WR}), S_8=(F_{WR},F_{wi},S_{UR}), S_9=(F_{WR},F_{wr}),$
$S_{11}=(F_{wr},F_{WI}), S_{12}=(F_{wr},F_{UI}), S_{13}=(F_{WR},F_{ui}), S_{14}=(F_{WR},F_{WI},S_{ur}),$
$S_{15}=(F_{ur},F_{WR}), S_{16}=(F_{ur},F_{WI})$

Notations and Symbols

E	The set of regenerative states
O	The unit is operative and in normal mode
CS	The unit is in cold-standby
CS_{nso}	Cold-standby not switched on
CS_{NSO}	Continuously in cold-standby from previous state
p/q	Probability that switch is working/failed
a/b	Probability that repair/ replacement is feasible after inspection
F_{ui}/F_{UI}	Failed unit under inspection /under inspection continuously from previous state
F_{wi}/F_{WI}	Failed unit waiting for inspection / waiting for inspection continuously from previous state

F_{ur} / F_{UR}	Failed unit under repair / under repair continuously from previous state
F_{wr} / F_{WR}	Failed unit waiting for repair / waiting for repair continuously from previous state
S_{ur} / S_{UR}	Failed switch under repair / under repair continuously from previous state
S_{wr} / S_{WR}	Failed switch under repair / under repair continuously from previous state
$z(t) / Z(t)$	pdf/ cdf of failure time of unit
$g(t) / G(t)$	pdf / cdf of inspection time upon cold standby failure
$f(t) / F(t)$	pdf / cdf of repair time of unit
$h(t) / H(t)$	pdf / cdf of repair time of switch
$s(t) / S(t)$	pdf/ cdf of failure time of cold standby unit (max. redundancy time)
$w(t) / W(t)$	pdf/ cdf of arrival time of server
$q_{ij}(t) / Q_{ij}(t)$	pdf/ cdf of direct transition time from regenerative state S_i to regenerative state S_j or failed state S_j without visiting any other regenerative state in $(0,t]$
$q_{ij.kr}(t) / Q_{ij.kr}(t)$	pdf/cdf of first passage time from regenerative state S_i to regenerative state S_j or failed state S_j visiting state S_k, S_r once in $(0,t]$
$\mu_i(t)$	Probability that the system up initially in state $S_i \in E$ is up at time t without visiting to any regenerative state
$[s]/[c]$	Symbol for Laplace-Stietjes convolution/Laplace convolution

Model Development

State Transition Diagram

By taking into account all possible transitions and the re-generative points, a systematic state transition diagram is constructed (Figure 1) where the solid dots represent the regenerative points (where system restarts itself probabilistically) for various states of the model.

Probabilities

Simple probabilistic considerations yield the following expressions for the non-zero elements

$$p_{ij} = Q_{ij}(\infty) = \int_0^\infty q_{ij}(t)dt = \tilde{Q}_{ij}(0)$$

$$p_{01} = \int_0^\infty pz(t)\bar{S}(t)dt,\ p_{02} = \int_0^\infty qz(t)\bar{S}(t)dt,\ p_{03} = \int_0^\infty s(t)\bar{Z}(t)dt,\ p_{14} = \int_0^\infty w(t)\bar{Z}(t)dt,\ p_{19} = \int_0^\infty z(t)\bar{W}(t)dt,$$

$$p_{26} = \int_0^\infty w(t)\bar{S}(t)dt,\ p_{27} = \int_0^\infty s(t)\bar{W}(t)dt,\ p_{35} = \int_0^\infty w(t)\bar{Z}(t)dt,\ p_{3,11} = \int_0^\infty z(t)\bar{W}(t)dt,$$

$$p_{40} = \int_0^\infty f(t)\bar{Z}(t)dt,\ p_{4,10} = \int_0^\infty z(t)\bar{F}(t)dt,\ p_{50} = \int_0^\infty bg(t)\bar{Z}(t)dt,\ p_{54} = \int_0^\infty ag(t)\bar{Z}dt,$$

$$p_{5,12} = \int_0^\infty z(t)\bar{G}(t)dt,\ p_{64} = \int_0^\infty h(t)\bar{S}(t)dt,\ p_{68} = \int_0^\infty s(t)\bar{H}(t)dt,\ p_{7,14} = \int_0^\infty w(t)dt,\ p_{8,16} = \int_0^\infty h(t)dt,$$

$$p_{9,15} = \int_0^\infty w(t)dt,\ p_{10,4} = \int_0^\infty f(t)dt,\ p_{11,13} = \int_0^\infty w(t)dt,\ p_{12,4} = \int_0^\infty bg(t)dt,\ p_{12,15} = \int_0^\infty ag(t)dt,$$

$p_{13,4}=\int_0^\infty bg(t)dt$, $p_{13,15}=\int_0^\infty ag(t)dt$, $p_{14,16}=\int_0^\infty h(t)dt$, $p_{15,4}=\int_0^\infty f(t)dt$, $p_{16,5}=\int_0^\infty f(t)dt$,

$p_{1,4.9,15}=p_{1,9}[c]p_{9,15}[c]p_{15,4}$, $p_{2,4.6}=p_{26}[c]p_{64}$, $p_{2,5.6,8,16}=p_{26}[c]p_{68}[c]p_{8,16}[c]p_{16,5}$,

$p_{2,5.7,14,16}=p_{27}[c]p_{7,14}[c]p_{14,16}[c]p_{16,5}$, $p_{3,4.11,13}=p_{3,11}[c]p_{11,13}[c]p_{13,4}$,

$p_{3,4.11,13,15}=p_{3,11}[c]p_{11,13}[c]p_{13,15}[c]p_{15,4}$, $p_{5,4.12}=p_{5,12}[c]p_{12,4}$, $p_{5,4.12,15}=p_{5,12}[c]p_{12,15}[c]p_{15,4}$

It can be easily verified that

$p_{01}+p_{02}+p_{03}=p_{14}+p_{19}=p_{26}+p_{27}=p_{35}+p_{3,11}=p_{40}+p_{4,10}=p_{50}+p_{54}+p_{5,12}=p_{64}+p_{68}$

$=p_{7,14}=p_{8,16}=p_{9,15}=p_{10,4}=p_{11,13}=p_{12,4}+p_{12,15}=p_{13,4}+p_{13,15}=p_{14,16}=p_{15,4}=p_{16,5}=1$

Mean Sojourn Times

The unconditional mean time taken by the system to transit to any regenerative state S_j when it (time) is counted from an epoch of entrance into that state S_i is given by

$$m_{ij}=\int_0^\infty td\{Q_{ij}(t)\}=-q_{ij}^{*'}(0)$$

And the mean sojourn time in the state S_i is given by

$$\mu_i=E(t)=\int_0^\infty P(T>t)dt$$

Where T denotes the time to system failure.

The General mean sojourn times are as

$\mu_0=\int_0^\infty \overline{Z}(t)\overline{S}(t)dt$, $\mu_1=\int_0^\infty \overline{W}(t)\overline{Z}(t)dt$, $\mu_2=\int_0^\infty \overline{W}(t)\overline{S}(t)dt$, $\mu_3=\int_0^\infty \overline{Z}(t)\overline{W}(t)dt$, $\mu_4=\int_0^\infty \overline{Z}(t)\overline{F}(t)dt$,

$\mu_5=\int_0^\infty \overline{G}(t)\overline{Z}(t)dt$, $\mu_6=\int_0^\infty \overline{S}(t)\overline{H}(t)dt$, $\mu_7=\mu_9=\mu_{11}=\int_0^\infty \overline{W}(t)dt$, $\mu_8=\mu_{14}=\int_0^\infty \overline{H}(t)dt$,

$\mu_{10}=\mu_{15}=\mu_{16}=\int_0^\infty \overline{F}(t)dt$, $\mu_{12}=\mu_{13}=\int_0^\infty \overline{G}(t)dt$, $\mu_1'=m_{14}+m_{1,4.9,15}$, $\mu_2'=m_{2,4.6}+m_{2,5.6,8,16}+m_{2,5.7,14,16}$,

$\mu_3'=m_{35}+m_{3,4.11,13}+m_{3,4.11,13,15}$, $\mu_4'=m_{40}+m_{4,4.10}$, $\mu_5'=m_{50}+m_{54}+m_{5,4.12}$,$+m_{5,4.12,15}$, Further

$\sum_j m_{ij}=\mu_i$

Reliability and Mean Time to System Failure (MTSF)

Let $\phi_i(t)$ be the cdf of the first passage time from regenerative state S_i to a failed state, regarding the failed state as an absorbing state, we have the following recursive relations for $\phi_i(t)$:

$\phi_0(t)=Q_{01}(t)[s]\phi_1(t)+Q_{02}(t)+Q_{03}(t)[s]\phi_3(t)$

$\phi_1(t)=Q_{14}(t)[s]\phi_4(t)+Q_{19}(t)$

$\phi_3(t)=Q_{35}(t)[s]\phi_5(t)+Q_{3,11}(t)$

$\phi_4(t)=Q_{40}(t)[s]\phi_0(t)+Q_{4,10}(t)$

$\phi_5(t)=Q_{50}(t)[s]\phi_0(t)+Q_{54}(t)[s]\phi_4(t)+Q_{5,12}(t)$ (1)

Taking LST of above relations (1) and solving for $\tilde{\phi}_0(s)$, we get

$$\tilde{\phi}_0(s) = \frac{\tilde{Q}_{01}(s)\{\tilde{Q}_{19}(s) + \tilde{Q}_{14}(s)\tilde{Q}_{4,10}(s)\} + \tilde{Q}_{02}(s) + \tilde{Q}_{03}(s)[\tilde{Q}_{3,11}(s) + \tilde{Q}_{35}(s)\{\tilde{Q}_{4,10}(s)\tilde{Q}_{54}(s) + \tilde{Q}_{5,12}(s)\}]}{1 - \tilde{Q}_{01}(s)\tilde{Q}_{14}(s)\tilde{Q}_{40}(s) - \tilde{Q}_{03}(s)\tilde{Q}_{35}(s)\{\tilde{Q}_{40}(s)\tilde{Q}_{54}(s) + \tilde{Q}_{50}(s)\}}$$

The mean time to system failure (MTSF) is given by

$$MTSF = \lim_{s\to 0} \frac{1-\tilde{\phi}_0(s)}{s} = \frac{\mu_0 + p_{01}\mu_1 + p_{03}\mu_3 + \{p_{01}p_{14} + p_{03}p_{35}p_{54}\}\mu_4 + p_{03}p_{35}\mu_5}{1 - p_{01}p_{14}p_{40} - p_{03}p_{35}\{p_{40}p_{54} + p_{50}\}} \quad (2)$$

The reliability of system model can be obtained as follows

$$R(t) = L^{-1}\left[\frac{1-\tilde{\phi}_0(s)}{s}\right] \quad (3)$$

Numerical Analysis

Particular case is considered for Weibull distribution with common shape parameter and different scale parameters as follows:

$z(t) = \alpha\eta t^{\eta-1}\exp(-\alpha t^{\eta})$, $g(t) = \lambda\eta t^{\eta-1}\exp(-\lambda t^{\eta})$,

$f(t) = \beta\eta t^{\eta-1}\exp(-\beta t^{\eta})$, $h(t) = \gamma\eta t^{\eta-1}\exp(-\gamma t^{\eta})$,

$s(t) = \mu\eta t^{\eta-1}\exp(-\mu t^{\eta})$, $w(t) = \delta\eta t^{\eta-1}\exp(-\delta t^{\eta})$

Where $t \geq 0$ and $\alpha, \lambda, \beta, \gamma, \mu, \delta, \eta > 0$

For the particular case of Weibull distribution we obtained the expression for mean time to system failure.

MTSF = N_1/D_1,

Where $N_1 = \Gamma\left(1+\frac{1}{\eta}\right)\left(\begin{array}{l}\{(\delta+\alpha)(\alpha+\beta)(\lambda+\alpha)\}^{\frac{1}{\eta}} + \{p\alpha+\mu\}(\alpha+\mu)^{\frac{1}{\eta}-1}\{(\alpha+\beta)(\lambda+\alpha)\}^{\frac{1}{\eta}} + \{p\alpha\delta \\ (\alpha+\lambda) + \mu\delta a\lambda\}\{(\alpha+\mu)(\lambda+\alpha)(\delta+\alpha)\}^{\frac{1}{\eta}-1} + \mu\delta\{(\alpha+\mu)(\delta+\alpha)\}^{\frac{1}{\eta}-1}(\alpha+\beta)^{\frac{1}{\eta}}\end{array}\right)$

$$\{(\alpha+\mu)(\alpha+\beta)(\lambda+\alpha)(\delta+\alpha)\}^{\frac{1}{\eta}}$$

$$D_1 = \frac{\left((\alpha+\mu)(\alpha+\beta)(\lambda+\alpha)(\alpha+\delta) - p\alpha\beta\delta(\alpha+\lambda) - \mu\delta\{\beta\lambda + \alpha b\lambda\}\right)}{(\alpha+\mu)(\alpha+\beta)(\alpha+\lambda)(\alpha+\delta)},$$

The system reliability in terms of MTSF is investigated by assigning some values to different parameters i.e. β=0.6,γ=0.7,λ=0.3,μ=0.01,p=0.4,q=0.6,a=0.3 and b=0.7.The behaviour of MTSF w.r.t the arrival rate of server and varied values of shape parameter are shown in tables 1, 2 and 3. All of the three tables show a declining trend of MTSF, as the failure rate of the unit (α) increases. We also observed that MTSF start increasing as we increase the arrival rate of server δ from 0.12 to 0.3. These tables illustrate that as shape parameter (η) increases the MTSF declines because the shape parameter of a Weibull distribution represents the various phases in the lifecycle of a system.

So it is evident that when the system is new it has the maximum MTSF and slowly and gradually when the system ages, MTSF decreases which result in the decline in the reliability. The present investigation recommends that there is a crucial need of quick server who performs all restoration tasks swiftly and effectively and contributes towards high reliability due to reduction in downtime.

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Table: Effect of the arrival rate of server on MTSF

Failure	MTSF (η=0.5)		MTSF (η=1)		MTSF (η=2)	
rate α	δ=0.12	δ=0.3	δ=0.12	δ=0.3	δ=0.12	δ=0.3
0.01	13622.29	14625.96	153.48	158.20	27.41	28.01
0.02	4460.51	4790.88	75.96	78.49	16.11	16.70
0.03	2202.01	2359.23	50.22	51.97	12.06	12.63
0.04	1309.17	1396.82	37.40	38.73	9.89	10.43
0.05	867.08	920.44	29.74	30.81	8.51	9.03
0.06	616.46	650.78	24.66	25.54	7.54	8.04
0.07	460.84	483.73	21.04	21.79	6.82	7.29
0.08	357.64	373.29	18.34	18.98	6.26	6.71
0.09	285.71	296.58	16.25	16.81	5.80	6.23
0.1	233.57	241.18	14.58	15.07	5.43	5.84

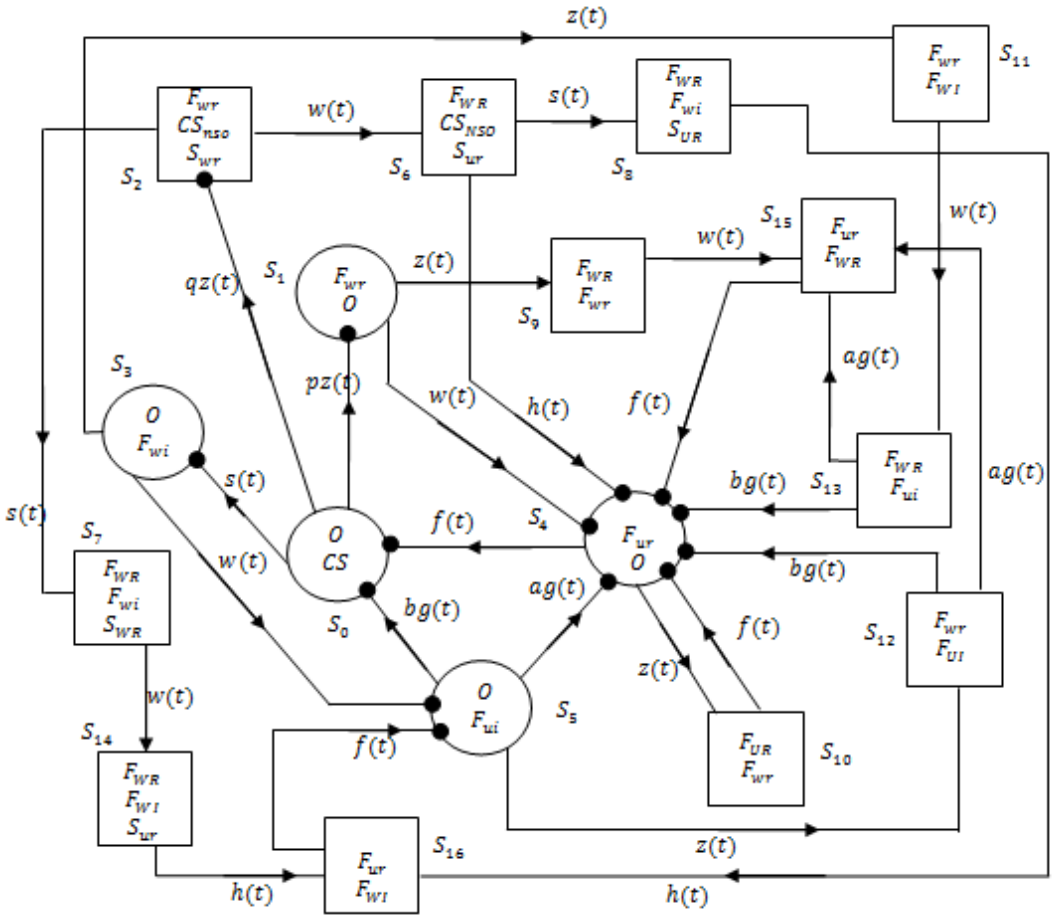

Figure 1: State transition diagram

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RESEARCH ARTICLE

Post Operative Management for Fracture Patients in Rehabilitation using IOT

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ABSTRACT

A hip fracture happens when the upper part of the thighbone (femur) breaks. The injury usually results from a fall or car accident. Hip fractures are more common in older people because bones weaken and become more brittle with age. Most hip fractures cause severe pain and require surgery immediately. Some people need a total hip replacement after a hip fracture. Physical therapy (PT) can improve the outlook for people with hip fractures.

Keywords: Operative management, Rehabilitation, Patients, Sensors

INTRODUCTION

Fractures of the hip are common. In the United States, more than 3k people fracture a hip every year. Risk factors for a hip fracture include: Age: Hip fractures are more common in people over 65. With age, bones break down, weaken and become more brittle. Older people are more likely to have problems with movement and balance, which can lead to a fall. Gender: Almost 1 to 45% of hip fractures happen to older women. Women lose bone mass after menopause. Weak bones are more likely to break. Lifestyle: People who live a sedentary lifestyle (don't get much exercise) are more likely to fracture a hip. Drinking too much alcohol can also weaken bones and increase your fracture risk. Medications: Some medications increase the risk of falls. Drugs that cause drowsiness or a drop in

blood pressure can cause you to lose your balance. Talk to your provider about taking these medications safely. Osteoporosis: This disease causes bones to become weak and porous, increasing the risk of fracture. Women are four times more likely to have osteoporosis than men.

Symptoms of a hip fracture

Symptoms of a hip fracture typically come on suddenly. But they can appear gradually and worsen with time. Signs of a hip fracture include: Pain: Usually, hip pain is severe and sharp. But it can also be mild or achy. Most people feel pain in the thigh, outer hip, pelvis and groin area. Pain may radiate down your buttock to your leg (sciatica). You may also feel pain in your knee. Limited mobility: Most people with a hip fracture can't stand or walk. Sometimes, it may be possible to walk, but it's extremely painful to put weight on the leg. Physical changes: You may have a bruise on your hip. One of your legs may appear shorter than the other. The hip might look like it's out of position, twisted or rotated.

Post operative recovery

Despite improvements in outcomes in recent years, hip fracture surgery remains high risk.1 This raises the question of whether patients with hip fracture should receive high dependency care after surgery, as would now routinely be the case for patients with a similar predicted mortality risk after emergency abdominal surgery. Adopting this approach on a universal basis would require resources that, at present, are unavailable in many healthcare systems. Other drawbacks include environmental factors in the critical care unit (e.g. monitors, alarms and frequent night-time interruptions), which may make delirium more likely in susceptible patients. We therefore suggest that postoperative critical care should be considered case-by-case for the management of specific reversible conditions, after risk assessment and in consultation with the multidisciplinary team. It is very important to provide a structured postoperative management pathway, aiming for early remobilisation, rehabilitation and maintenance of the patient's prior cognitive function. This approach is probably more important than providing postoperative critical care. The early involvement of orthogeriatricians, occupational therapists and physiotherapists is important, and postoperative screening for delirium as specified in the English BPT facilitates the early management of cognitive problems. Anaesthetists should be mindful of enabling postoperative recovery through their anaesthetic technique. To this end, there is an argument for providing anaesthesia in a consistent way on an institutional basis, so that those involved in recovery and rehabilitation after hip fracture are better able to anticipate patients' postoperative needs.

Although external fixation is being widely used by orthopaedic surgeons in the treatment of bone fractures, the surgical procedure and recovery are still followed by a number of possible complications which can significantly decrease the treatment's efficiency (cost) and effectiveness (optimal healing). Inability of the physician to have continuous insight into different data, fracture healing process, patient's behaviour and environmental factors could be considered as a reason for these complications. In this paper, we propose the improvement of a fixation device design, which implements paradigms of aware, sensing, smart and active devices and thus, enables real-time monitoring of bone fracture healing. Such a design is considered as IoT gateway, capable to classify occurrences of events and milestones in patient recovery process, based on the data from different sensors, and report those to the specialists or related Healthcare Information System. The design is implemented in the example of classifying patient's compliance to the prescribed behaviour in the postoperative treatment of bone fractures.

Besides industrial ones, IoT technologies are today increasingly used to address some of the major societal problems, in the domains of environment, healthcare and others. IoT technologies facilitate event detection, trend identification, data tracking and other functions. They enrich the principles of automatic sensing and control with continuous accessibility. Exactly that is one of the vital requirements for a remote healthcare. Real-time patient monitoring systems help to improve the diagnostics (based on data collected in real life situations, in a relevant time range), to identify clinical emergency and to monitor the therapeutic process. They are especially important in cases when patients are monitored and even treated remotely, such as in a homecare or small rural medical units [1]. Many different signals of physiological origin can be tracked: pulse oximetry, respiration rate, temperature, heart rate,

heart rate variability, arterial blood pressure, skin temperature, skin conductance, blood alcohol concentration, and others [1]. They can be combined with environmental (air temperature, humidity, atmospheric pressure) and location data to feed the processing algorithms which can infer the features indicative to a person health status.

This data, in raw, condensed or processed form can be accessed by the physician on demand. To a certain extent, such insight can reduce the need for periodical outpatient controls. Obviously, this can positively affect the cost of the healthcare and even reduce possible inconveniences for the patient. Furthermore, IoT device can be used as a closed-loop control system [3][4]; namely, in addition to sensors and transmitters, it can host actuators, which can be used to further decrease the cost of the therapy process. Various types of actuators can be added to IoT device, or act as independent units, namely device triggers, alarms, pacemakers, drug dispensers, insulin pumps, etc. This paper explores the use of IoT technologies in the field of orthopaedics. Motivation was related to resolving some issues of using external orthopedic fixation devices for healing bone injuries and in leg extension treatment [6]. More specifically, IoT paradigm is used to design the system which would reduce the risks and associated costs of homecare recovery of the patients with bone fractures, by facilitating real-time monitoring of relevant data and classification of healing progress milestone and disturbance events. Some external fixation device are simple mechanical structures, consisting of a rod (often of variable length) with other attached components, which is mounted on the parts of the fractured bone, by using two or more pins (see Figure 1). Rod is aimed to hold parts of the fractured bone and, before formation of callus (first formation of the new, soft bone tissue) at the fracture gap between bone fragments, the rod is receiving full load resulting from body weight. In time, newly formed bone tissue will reach the mechanical properties of the healthy bone and it will be able to take over the load back from the fixation device rod. At that time, the fixation device is being removed from the patient. Besides fracture healing, the similar treatment is used in the leg extension procedures.

Main condition for realizing current requirements for effective, efficient, customized healthcare is to achieve access to vast data about the patient's pre-conditions, current health status, as well as his/her environment. Such access, combined with advanced data interpretation algorithms, facilitates accurate diagnoses and real-time decisions in treatment fine tuning and customization. The example of ASSA orthopaedic fixation device aims at demonstrating how the above can be achieved by using IoT technologies and approaches. In this paper, we have shown how the device makes possible to make real-time observations on behaviour of the patient with fractured tibia in a homecare.

Those observations can be easily used to: Alert the patient on the activities of high risk, namely intentional or incidental running, stairs climbing. Advise the patient on adjusting the prescribed behaviour or exercises, for example, increase or decrease load of the fractured leg during the walk or stand with crutches. Determine the cause of the mechanical issues in fixation device after their occurrences. The realization of above would surely have an impact to the treatment process, first of all by reducing the incidence of the complications occurrences. More important, realization of other functionalities would make the treatment more effective and efficient by enabling better treatment planning, fully based on actual healing progress data. Part of this work aimed at developing activity recognition methodology (including the segmentation method, algorithm and features' selection) for a single accelerometer placed on a calf position. The work will be extended in the future to recognize other types of activities (combined with the load sensor data), namely the other specific exercises typically prescribed to the patients with externally fixated tibia. Additional efforts will be put to increase the accuracy of the individual activities' recognition, by introducing new features or by using new features' combinations. The next step will be to design and develop an integrated solution, namely a prototype of the ASSA device, including also interoperable IoT platform. Some initial steps have been already made in this direction [30]. Finally, other capabilities of the ASSA device will be addressed. The potential for reuse of the reported research results is significant. The proposed architecture, with different sensing capabilities can be applied in a wide range of Ambient Assisted Living (AAL) platforms [32], which address the health care of aging and/or incapacitated individuals in a home care. The implemented system can be replicated in different data feature extraction and classification cases, such as monitoring of different cardiac diseases, based on electrocardiogram (ECG) data [33].

Post Operative Physiotherapy

It is essential to retrain muscles and often very specific strengthening is needed to achieve a full recovery after a surgery. Common Surgeries requiring Post-Operative Physiotherapy Care are:

- Joint replacement: Knee replacement (TKR, PKR), Hip replacement surgeries (THR)
- Shoulder: Shoulder Reconstruction, Shoulder Stabilisation, Rotator Cuff Repair, Acromioplasty, Manipulation, Capsulotomy, Fracture
- Spine (Neck & Back): Discectomy, Micro-discectomy, Laminectomy, Spinal Fusion/Stabilisation
- Elbow: Tennis Elbow Release, Golfers Elbow Release, Fracture
- Wrist & Hand: Carpal Tunnel Release, Fracture, Tendon Repairs
- Knee: ACL and Ligament Reconstruction, Arthroscope, Meniscal Repairs, Chondroplasty, Lateral Release, Patella Tendon Transfer, Fracture apart from TKR
- Calf: Achilles Tendon Repairs, Fasciotomy
- Ankle & Foot: Ankle Reconstruction, Ligament Repairs, Arthroscope, Fracture, Spur Removal, Bunionectomy

Rehabilitation Pathway Category of care

Frailty Undertake frailty assessment, instigate interventions as appropriate, involve patient in establishing goals to maximise function and achieve safe discharge. Activities of daily living Ensure progression in recovery of pre-fracture level of independence, aiming for further improvement depending on tolerance Assess need for aids and develop strategies to improve independence Demonstrate safe transfer using aids and equipment as appropriate Ensure there is adequate support in the home environment in terms of assistance from a caregiver or service Recommend the family consider a medical alert system if available and appropriate *Bathing and grooming*: Encourage and support independence, bathing and grooming out of bed with assistance if necessary *Dressing*: Support getting out of bed and dressed daily, using dressing aids as necessary *Toileting*: Encourage regular toileting to promote continence, toileting should be in the bathroom, not using bedpans or urinals *Eating*: A high protein/calorie diet should be continued and meals taken in a chair or dining room. An oral nutritional supplement should be considered Support for activities of daily living should be provided after discharge. Appropriate home equipment should be provided (mobility aid, raised toilet seat and toilet surround and other items as required).Mobility Consider conducting an assessment of mobility/activities of daily living to enable monitoring of recovery of mobility (e.g. the Timed Up and Go test, Barthel Index of Activities of Daily Living) Exercise incorporating strengthening, balance and functional components should be continued after discharge Walking with or without an aid for at least 50–100 m should be undertaken at least three times daily, or as appropriate depending on pre-fracture mobility Capacity to walk the distance required to attend meals in the home setting should be demonstrated Ensure ability to manage stairs if necessary and to mobilise safely outside the home in all weather conditions, uneven surfaces, curbs, etc. Arrange further mobility training after hospital discharge. Medications A review of all medications should have been undertaken on admission, polypharmacy should be addressed Use of sedatives and antipsychotics should be minimised or ceased and doses should be regularly reviewed Medication should be adequate for pain control to enable optimal independence in activities of daily living

Cognitive and mental status

IoT-based Strategies to prevent and treat delirium should be continued, including ensuring appropriate use of vision and hearing aids, fluid enhancement, orientation, optimising mobility and non-pharmacological sleep supporting strategies. Behaviour monitoring should be undertaken if necessary Activity should be encouraged for those with dementia or depression, in terms of ambulation, exercise and social participation Caregivers should be provided with support and access to community Prevention of further falls/ fractures resources as appropriate Pos Osteoporosis management should be considered if this hasn't already occurred and continued post-discharge Fall prevention strategies should be instigated and the use of hip protectors. The goal of rehabilitation is to achieve the maximum potential for function and normal activities. It consists of a procedure in which the patient improves the mobility progressively and increases the strength of the joint or muscle affected. Therapeutic robotics seems to

accelerate the rehabilitation process due to its accuracy. Thus, we have considered the design of a prototype controlled by the computer for the rehabilitation of the wrist and elbow of an adult. The patient will exercise in a passive way to achieve the full range of motion of the joints of the elbow and wrist during the first and second phases of rehabilitation.

Electronic Design

The electronic design is composed of two main areas. A sensors' interface electronic board and a control board are in charge of all the actions executed by the actuator. The circuits for the signal conditioning of the sensors of the angular position, sense of rotation and limit switches status are in the sensors' interface board. Meanwhile, the board control is an Arduino board which was selected by the number of Input/Output (I/O) pins needed for this project. Because of the 14 I/O pins and the Pulse-Width Modulation (PWM) outputs necessary to control the Torxis servo IoT board was selected to be used as the controller in this project.

Electronic Diagram

The interface of the user programming allows the input rehabilitation data, movement selection, angular limits for each movement, motor calibration and status verification of the sensors. Consequently, the programming has been divided into two different processes which are the maintenance and the rehabilitation process, The user chooses which process to execute between calibration of the servo and verification of the status of the sensors by selecting the corresponding option. The maintenance interface. To complete the rehabilitation process, the user should follow these steps:

Zone to rehabilitate (Elbow or Wrist).

Arm to rehabilitate (Left or Right).

Movement to execute (Flexion-Extension, Pronation-Supination, Flexion- Extension, Abduction-Adduction).

Duty cycle input (Minimum and maximum angles, number of sets and repetitions, speed).

CONCLUSION

The testing done on a patient diagnosed with elbow and wrist fracture test, it may be concluded that the patient improved in the mobility of both joints using the rehabilitation prototype, within several days. Therefore, this project fulfilled the goal of progressively improving the mobility of the complete angular range of the corresponding movement. It is important to mention that due to the degree of pain and nature of lesion that the patient presented, she could only perform flexion-extension of the wrist and pronation-supination of the elbow.

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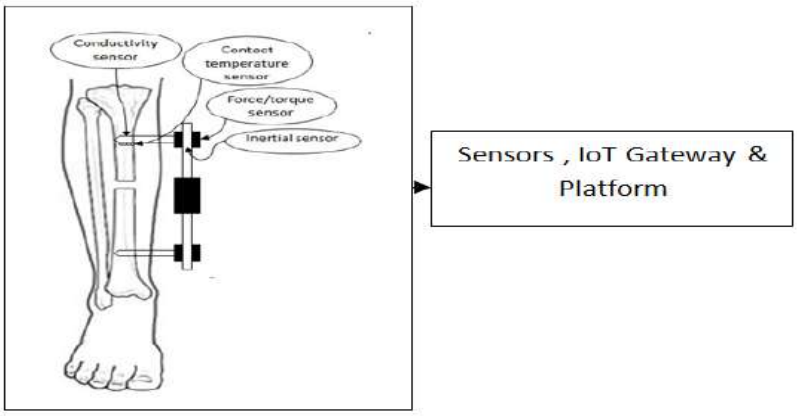

Fig 1: Basic architecture of device IoT system

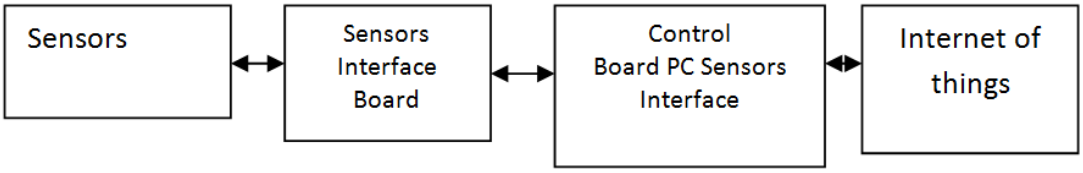

Fig 2: Electronic Diagram

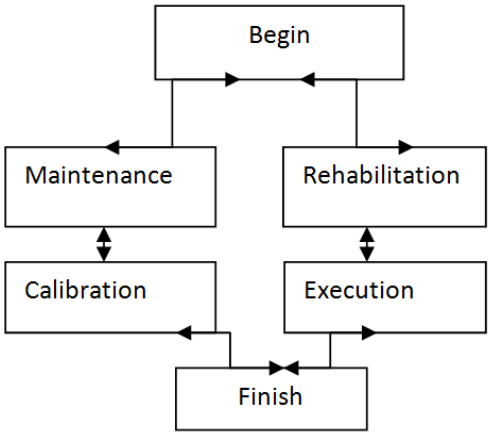

Fig 3: Flow diagram

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RESEARCH ARTICLE

An Analysis and Alert System for Imbalanced Weight Distribution of Sitting Posture

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ABSTRACT

Sitting in a chair for long periods of time can definitely cause low back pain or worsen an existing back problem, no matter how comfortable the chair is. The main reason behind is that, static posture increases stress in the back, shoulders, arms, and legs, and in particular, can add large amounts of pressure to the back muscles and spinal discs. The sitting posture is characterized by changes in body configuration and weight-bearing compared with the standing posture. The system is incorporated with a load cell weight balance to display and alert regarding the present sitting position to be adjusted for a normal user, so that he/she will be in good sitting posture. The system can also be used for the patients who are affected with paralysis and other disabilities, with a front body fastening belt and forearm support board.

Keywords: Load cell, Weight balance, Sitting posture, Static posture, Forearm support board, Fastening belt.

INTRODUCTION

'In present scenario majority of people suffers from several spinal cord problems because of prolonged wrong sitting posture. Maximum of people spend hours and hours by sitting in work basis, watching television, working in laptops or long travel, may subjected to get spinal problems. Moreover prolonged seating position may lead to physical and mental exhaustion. Physical exhaustion leads to muscle stiffness, numbness, shoulder pain, neck pain or cramp, however mental exhaustion may lead to depression, raising blood pressure, cholesterol or sugar level and it may risk their own lives. Although there are many methods and treatments are available to get rid of this problem, but still there is a strong need for preventive actions. So this proposed system will help us to be cautious in our sitting posture.

Literature review

Sitting Posture Analysis

According to a study published in 2013 by the Mayo Clinic, back pain is the third most common cause of doctor visits in the United States. And according to American Family Physician, only 25 to 30% of people seek treatment for their back pain. The most common cause of lower back pain is postural stress. For this reason, lower back pain is frequently brought on by sleeping in the wrong position, prolonged bending, heavy lifting, or even standing or laying down in a poor, rounded-back position. According to Cornell University Department of Ergonomics, up to 90% more pressure is put on your back when you sit versus when you stand. This applies to sitting at work, in the car, and at home. Dr. Joan Vernikos, former director of NASA's Life Sciences Division and author of the "Sitting Kills, Moving Heals" explain, "We weren't designed to sit. The body is a perpetual motion machine." When you're sedentary, your muscles get less oxygen and nutrients from your blood.

People Behavioural Analysis: Although there has been renewed research interest in the study of sedentary behaviour, evidence linking occupational sitting to cardiovascular health dates back to the pioneering work of Jerry Morris in the 1950s. In a seminal epidemiologic study, Dr. Morris and his colleagues found that seated workers (London bus drivers and mail sorters) had higher rates of cardiovascular events than employees who stood and walked while working (ticket collectors and postal workers). Until recently, the health risks associated with a sedentary lifestyle were thought to be a result of insufficient moderate-to-vigorous physical activity, leading many to incorrectly assume that sedentary behaviour and physical activity were opposite ends of the same continuum.

Over the past 5 years, state-of-the-science papers on inactivity physiology have been published by Marc Hamilton and colleagues, 7–9 who have started to piece together a compelling case that different physiologic mechanisms may be operating during periods of muscular unloading compared to periods of exercise. Physiologic mechanisms observed during periods of inactivity may have an indirect influence on our cardio metabolic health because of their role in triglyceride uptake, HDL cholesterol production, and glucose transport. The research literature on sedentary behaviour and health has been dominated by studies about relationships between TV viewing and pediatric obesity. Studies on the deleterious effects of prolonged sitting during adulthood have only recently started to emerge.

METHODOLOGY

The system includes several load cell sensors to measure the sitting posture of user seated on a chair. An alert along with the position to be adjusted is given if the user has not seated in proper position. Upon receiving the alert signal the user can intently change the sitting position to avoid discomforts like stress back, hip, shoulders, neck and arm. This proposal's main goal is to

- Monitors sitting and leaning posture of user
- Display the sitting and leaning posture of the user by using weighing sensors
- Alert the user to sit in correct position

Design: The system is designed using several load cell sensors and pre-amplifiers used to detect the balanced weight distribution of user while sitting in the chair. The data is processed and imbalance in the weight distribution is alerted so that the user can correct the sitting posture.

Implementation: This is a collaborative proposal between Engineering stream and Physiotherapy Stream. The problem is identified in human physio exercise so a Co-PI is selected from a Physiotherapy Stream in order to execute this proposal.

- Sitting and leaning posture of user is monitored and the result is displayed.
- Alert message is given to the user to correct his/her sitting posture.

This is designed for the users to self correct his/her sitting posture in order to avoid physical stresses. Maximum of spinal cord pain is occurring due to wrong sitting, standing and sleeping postures.

Design of the System: We will discuss our method for tracking the postures of smart wheelchair users in the next sections. We created a smart cushion in especially to track sitting postures. The technology can be used to create a smart wheelchair system that can, for example, warn the user of long-term incorrect/dangerous postures and, in emergency scenarios, alert relatives and careers to aid the assisted user as soon as possible. Fig 2.The proposed system's core is the posture detection layer, which has already been created; many application services outside the scope of this work can be readily built on top of it. The proposed system's core is the posture detection layer, which has already been created; many application services outside the scope of this work can be readily built on top of it. The Posture Detection Layer consists of two subsystems. The Sensing subsystem, which collects data generated by the weight of the body using pressure sensors mounted on the wheelchair. Several (mobile and cloud-based) apps can be built on top of the posture recognition subsystem to locate the user using geo-location via dedicated mobile device services (such as GPS, WiFi, or cellular tower signal strength).Applications can show sensing findings, analyse activity levels, warn users about risky postures, and, if necessary, convey the user's location and make emergency automatic voice calls to carers.

FUTURE PLANS

In future this may be extending to monitor persons working in information technology firms, etc. The work may be extend to alert standing and sleeping postures.

CONCLUSION

This research focuses on a cushion-based wheelchair assist system for mobility-impaired individuals that can recognise positions. Pressure sensors are utilised to collect data on the wheelchair user's postures, different classification methods have been compared to find an efficient classifier, and previous sensor deployment methods have been compared to find the best deployment method. In addition, the study discusses several practical applications. The system can promptly send a warning if unsafe scenarios such as long-term improper posture are detected; also, posture detection is a basic block towards activity level evaluation. To more correctly detect sitting postures, an optimization method of pressure sensor deployment is proposed. The best posture classifier based on pressure sensors' smart cushion was identified after an in-depth evaluation of many classification algorithms. In contrast to earlier research, the BMI is one of the criteria taken into account while evaluating the applicability and robustness of the proposed deployment strategy across various body forms.

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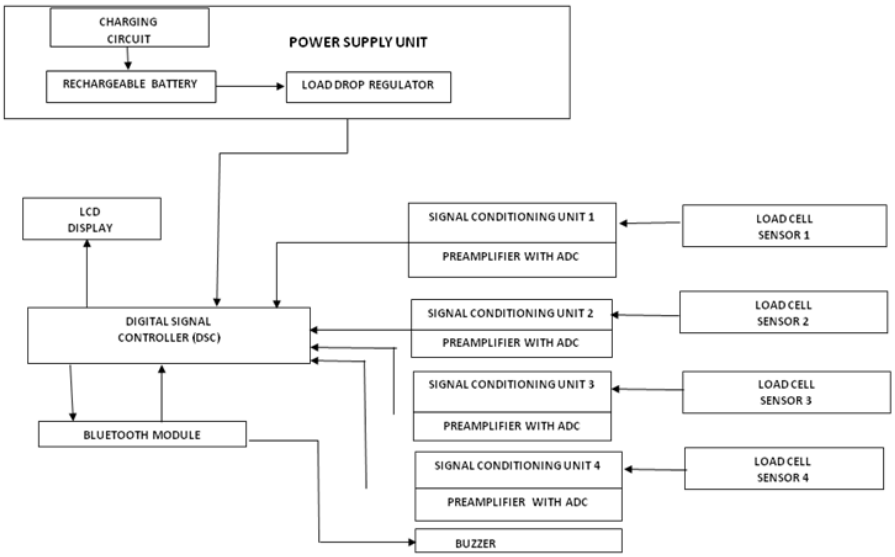

Fig 1: Analysis and Alert System for Imbalanced Weight Distribution of Sitting Posture

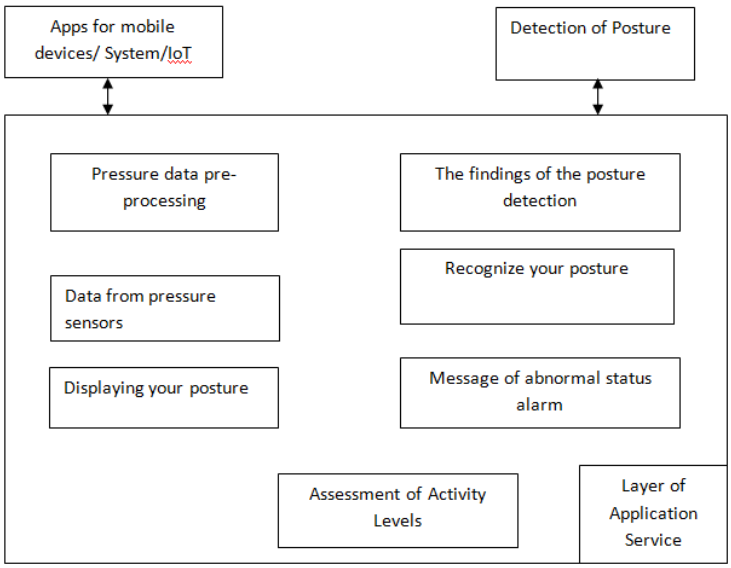

Fig 2: Design of the System

Fig 3: Design Kit - An Analysis and Alert System for Imbalanced Weight Distribution of Sitting Posture

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RESEARCH ARTICLE

Experimental Invesgation On Fire Brick Behaiviour using in Building Construction

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ABSTRACT

India is a rapidly developing country with a high demand for new structures and the demolition of old ones due to increased urbanisation. Every year, the construction sector generates a large amount of destroyed trash. Repurposing this demolished waste minimises carbon emissions and ensures a long-term construction project. In this initiative, an effort has been made to use demolished trash in the production of solid bricks. This study explores the qualities of bricks, including both strength and aesthetic testing such as water absorption and compressive tests, which will be conducted on bricks made from construction debris and regular bricks. This project is really beneficial because it is environmentally friendly.

Keywords: Bricks, Building Construction **,** solid waste , Recycling.

INTRODUCTION

As infrastructural developments are the ground for any country to tread in growth, the demand for building materials is also consistent on its hike. The storage or dumping of the construction debris is the merging problem in the solid waste management. The earth or soil available for the manufacture of the bricks is present in very less quantity over the earth`s crust. At the same time the agriculture depends on the quantity and quality of the soil for any of its products. If the soil is burnt for the manufacture of the bricks, it cannot be reused for agriculture. The burnt soil would become non bio-degradable material as plastics. So, an alternative material has to be found. The

construction waste which is called as solid waste may be used for the production of the bricks. This project attends to reuse the construction wastes in the construction industry.

Construction and demolition (C&D) waste is generated whenever any construction and demolition activities take place such as building, bridges, roads flyover, malls and by the demolition of old buildings, widening of roads, remodeling, etc. C & D material consists mostly of inert and non-biodegradable material such as concrete, plaster, metal, plastics etc. These wastes are heavy, bulky and occupy considerable space in huge amount on the road sides. It is estimated that the construction sector in India generates about 10-12 million tons of wastes annually, it is more often dumped in open and low-lying areas; however, recent recognition of the potential for diversion of waste components from landfills has laid C&D waste becoming a topic of interest for recycling.

Literature Collections

J.N Akhtar & M.N Akhtar: Bricks with Total Replacement of Clay by Fly Ash Mixed with Different Materials.Fly ash is a powdery substance obtained from the dust collectors in the thermal power plants that use coal as fuel. From the cement point of view the mineralogy of Fly ash is important as it contains 80% - 90% of glass. The impurities in coal-mostly clays, shale's, limestone& dolomite; they cannot be burned so they turn up as ash. The Fly ash of class C category was used as a raw material to total replacement of clay for making Fly ash bricks. In present study the effect of Fly ash with high replacement of clay mixed with different materials were studied at a constant percentage of cement i.e 10%. Three Categories of bricks were to be studied namely Plain Fly ash brick (FAB), Treated Fly ash brick (TFAB) and Treated Fly ash stone dust brick (TFASDB).In all the above mentioned categories the quantity of Fly ash was kept constant as 80%. It is found that the compressive strength of plain Fly ash brick (15FAB) and Treated Fly ash brick (15TFAB) was found to be higher with 5% coarse sand and 15% sand combination at 10% cement. The gain in strength continues for Treated Fly ash Stone dust Brick (10TFASDB) and found to be higher with 10% stone dust and 10% sand combination.

A variationin the quantity of Fly ash was also attempted and it was found that the 25TFASDB with 50% fly ash, 25% stone dust and 25% sand combination at 10% cement achieved highest compressive strength. The addition of lime to the fly ash increases the cementitious properties of Fly ash and it was found that at 1.5% of lime, the OMC is minimum and dry density maximum. The compressive strength of Treated Fly Ash Brick (15TFAB) is more than Plain Fly Ash Brick (15FAB). The compressive strength of Treated Fly Ash Stone Dust Brick (10TFASDB) is more than 15FAB and 15TFAB. Treated Fly Ash Stone Dust Brick designated as (25TFASDB) achieved highest compressive strength ($79Kg/cm^2$) with 25% stone dust, 25% sand and 50% treated fly ash combination at 10 % cement as compared to15FAB, 15TFAB, 10TFASDB. Though the highest compressive strength ($79Kg/cm^2$) obtained in case of 25TFASDB is less than the maximum strength ($105Kg/cm^2$) of standard Ist class brick, even than the study is important as it replaces 50% of top soil by fly ash. More over the 25TFASDB bricks can be safely used in frame structure buildings as non-load bearing walls and also as load bearing walls in case of single-story constructions.

MATERIAL COLLECTION

Fine Aggregate

Generally River Sand is used in the Geo polymer brick. Natural or River sand are weathered and worn-out particles of rocks and are of various grades or sizes depending upon the amount of wearing. Now-a-days good sand is not readily available, it is transported from a long distance. Those resources are also exhausting very rapidly. So it is a need of the time to find some substitute to natural river sand. The artificial sand produced by proper machines can be a better substitute to river sand. When fine particles are in proper proportion, the sand will have fewer voids. The cement quantity required will be less. Such sand will be more economical. Demand for manufactured fine aggregates

for making brick is increasing day by day as river sand cannot meet the rising demand of construction sector. Because of its limited supply, the cost of Natural River sand has sky rocketed and its consistent supply cannot be guaranteed. Under this circumstances use of manufactured sand becomes inevitable. River sand in many parts of the country is not graded properly and has excessive silt and organic impurities and these can be detrimental to durability of steel in brick whereas manufactured sand has no silt or organic impurities

Construction and Demolition Waste

Classification of Waste:

- Residential
- Industrial
- Commercial
- Institutional
- C&D

Amount of C&D waste as per types:

- Based on structure type (Residential, Commercial, Industrial, Institutional)
- Based on structure size (Heavy, Med, Light)
- Activity being performed

Collection of C&D Waste:

- Collection of the C&DW can be done by the trucks having container of different sizes.
- Size of the container depends upon the demolition area/part.
- For handling very large volumes, front-end loaders in combination with sturdy tipper trucks may be used so that the time taken for loading and unloading is kept to the minimum.
- For small generators of construction debris, e.g., petty repair/maintenance job, there may be two options – (i) specific places for such dumping by the local body and (ii) removal on payment basis.
- In case of small towns where skips and tipping trailers are not available, manual loading and unloading should be permitted.
- In case of large towns where C&D waste generates in large amount, Zoning of the towns is necessary. By multiple pickup points of C&D waste we can easily do collection of C&D waste in large cities.
- Close co-ordination between the Sanitary Department, Municipal Engineering Department and Town Planning Department is essential if there is no consolidated Solid Waste Management Department to take care of the construction and demolition waste in addition to other municipal garbage.

TEST RESULTS

Water Absorption Test

The test was carried out by immersing the bricks in cold water for 24 hours after that its change in weight is calculated for water absorption. Water absorption percentage after 24 hrs immersion in cold water is given by the formula, $W = \{(M2- M1)/ (M1)\} \times 100$

CONCLUSION

The study aimed at the use of alternative material (demolished or recycled waste) for new construction, which is beleaguered with normal waste in terms of debris, dust, rubbish etc. in place of conventional material. The color, shape, size and texture of the bricks were found to be satisfactory. The water absorption property of all the bricks manufactured with construction debris is greater than the water absorption value of normal burnt bricks. It is in accordance with IS code standards. The compressive strength of the bricks manufactured with construction debris is found to be greater strong as compared to the normal burnt bricks. The amount of efflorescence is found to the grey deposit is less than 8 %. in debris bricks as compared to the normal burnt brick.

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Table 1 : Water Absorption Test

Mix Composition	Weight (gm)		Water Absorption (%)
	Dry (M_1)	Wet(M_2)	
Red soil brick	4.628	5.427	15.34
(Mix 1)	5.246	5.764	17.28
(Mix 2)	**5.642**	**5.928**	**17.84**

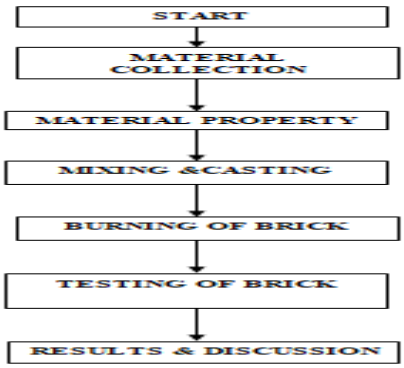

Fig. 1 Methodology

Fig. 2. Fine Aggregate

Fig.3. Demolition Waste

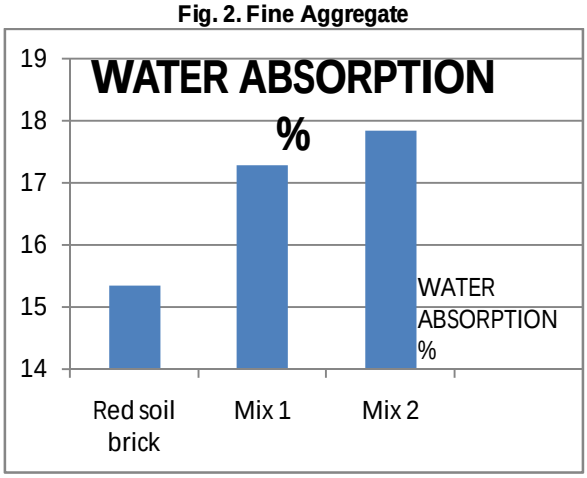

Fig.4. Water absorption test

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RESEARCH ARTICLE

Comparative Study of Various Deep Learning Models for Plant Leaf Disease Detection and Classification

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ABSTRACT

In the current situation, a variety of illnesses are attacking nearly all of the crop's leaves at an alarming rate. We used a tomato plant to detect and classify several leaf diseases in tomato plants [5] using a deep learning framework in this paper. There are a variety of pre-trained models for image classification, including one that uses a Convolution Neural Network (CNN) to improve the efficacy of leave illness classification. With Tensor Flow as a backend, the proposed model uses Keras sequential model, RMS prop optimizer, Rectified Linear Activation Unit (ReLU), and Softmax. This model's output is compared to that of other pre-trained models such as the VGG-16 model and ResNet50, and it is discovered that the suggested model's average testing accuracy is superior to that of other pre-trained models, at around 94.63 percent with less than 1% loss.

Keywords: Convolution Neural Networks (CNN), ResNet-50, VGG-16, Pre-trained model, Deep learning models.

INTRODUCTION

In artificial intelligence (AI) [3] and machine learning, deep learning models emerge as a new learning theory. Recent breakthroughs in image and data analysis have sparked substantial interest in this topic, despite the fact that applications from other disciplines are flooding the big data arena. On the negative,

the mathematical and computational technology that underpins deep learning models is extremely difficult to grasp, particularly for interdisciplinary researchers. As a result, we give in this paper a full report on the comparative research of various deep learning model methods, such as Convolution Neural Networks (CNNs), VGG-16 model, and ResNet50 model, as these models currently represent the major core architectures of deep learning models. These models have been developed to detect disease in plant leaves [2]. We're going to take a look at a tomato leaf.

Literature Review

Various studies have been conducted to establish various architecture models for the prediction of plant leaf disease with enhanced performance. We used multiple deep learning models in this research, which are extensively used in extracting high-level abstract characteristics, offering better performance than traditional models, boosting interpretability, and also for comprehending and processing biological data.We need an important strategy to expedite the training process with distributed computing and powerful computing resources like clusters and Graphical Processing Units in order to train large-scale deep learning models faster (GPUs). Data parallel, model parallel, and data-model parallel are some of the available parallel training methodologies. However, large-scale training necessitates deep models with varying efficiency for parameter synchronisation, which necessitates frequent communications between multiple computing nodes, such as separate server nodes in a distributed system, and heterogeneous computing systems with CPUs and GPUs. Furthermore, the memory constraints of contemporary GPUs may limit the scalability of deep networks. In large-scale deep learning networks, optimization and workload computing are major challenges, and with each development and design iteration of the deep learning model, not only the structure of the input data but also the model itself is likely to change. As a result, a one-time memory creation based on a fixed shape is insufficient, and most deep learning frameworks now use a dynamic memory allocation mechanism, so we're comparing the Convolution Neural Networks (CNN)[1], VGG 16, and ResNet50 deep models to see how well they perform in terms of accuracy. The current situation in identifying plant leaf diseases [2], [4], [5] is becoming increasingly relevant as a study topic in the agricultural area, as demand for healthy food drives production. Various technologies [3] have been used to monitor plant health using scientific imaging methods in order to quantify the strain on plants caused by pests, insufficient soil nutrients, and UV radiation, but there have been numerous drawbacks.

ResNet50 Architecture

ResNet50's architecture contains four stages, as shown in Figure 1.The network can accept an image with a height and width that are multiples of 32 and a channel width of 3.We'll assume the input size is 224 x 224 x 3 for the sake of clarity. Every ResNet design uses 77% and 33% kernel sizes for initial convolution and max-pooling, respectively. After that, Stage 1 of the network begins, which consists of three Residual blocks, each with three layers. The kernels used to perform the convolution process in all three layers of stage 1's block are 64, 64, and 128 bits in size, respectively. The identity relationship is represented by the curved arrows. The dashed connecting arrow indicates that the convolution operation in the Residual Block is conducted with stride 2, resulting in a half-size input in terms of height and breadth but a doubling channel width. The channel width is doubled and the size of the input is reduced to half as we advance from one stage to the next. ResNet's primary features are as follows:

- Batch Normalization is at the heart of ResNet.
- Batch Normalization improves the network's performance by adjusting the input layer.The issue of covariate shift has been solved.
- ResNet employs the Identity Connection, which aids in preventing the network from succumbing to the vanishing gradient problem.
- To improve network performance, the Deep Residual Network employs bottleneck residual block architecture.

Visual Geometry Group (VGG) – 16

VGG-16 is a deep CNN network with 16 convolution layers and a uniform architecture that was first published in 2015.The Visual Geometry Group (VGG) investigates the impact of increasing the depth of a convolution network on its accuracy in this paper. They employ architecture with very small convolution filters of size 3 3, which outperforms state-of-the-art setups by a factor of three. VGGNet comes in a variety of flavours (VGG16, VGG19, and so on) that differ solely in the total number of layers in the network. The VGG-16 Architecture is depicted in Figure 2 as a pictorial depiction. The input to the cov1 layer is a fixed-size 224 x 224 RGB picture that is processed through a stack of convolutional (conv.) layers with a very narrow receptive field: 33% (the smallest size to capture the notions of left/right, up/down, and centre).It also uses 11 convolution filters in one of the setups, which may be thought of as a linear transformation of the input channels (followed by non-linearity). The convolution stride is set to 1 pixel, and the spatial padding of conv. layer input is set to 1 pixel for 33 conv. layers so that the spatial resolution is kept after convolution. Five max-pooling layers, which follow part of the conv. layers, do spatial pooling (not all the conv. layers are followed by max-pooling).Max-pooling is done with stride 2 over a 22 pixel window.

Following a stack of convolutional layers (of varying depth in different topologies), three Fully-Connected (FC) layers are added: the first two have 4096 channels each, the third conducts 1000-way ILSVRC classification and so has 1000 channels (one for each class). The soft-max layer is the final layer. In all networks, the configuration of the fully connected with 16 layers is the same.

Proposed Convolutional Neural Network (CNN) Model

Convolutional Neural Networks (CNNs) [1] are a type of Feed forward Neural Network that employs convolution, ReLU, and pooling layers. Feed forward Neural Network components such as convolution, pooling, and fully-connected layers are typically found in standard CNNs. Each neuron in a layer is typically connected to all neurons in the following layer in classic ANNs, whereas each connection represents a network parameter. As a result, a significant number of parameters may be generated. A CNN, rather of employing fully connected layers, uses local connectivity between neurons, in which a neuron is only connected to neurons in the next layer that are close. The overall number of parameters in the network can be greatly reduced as a result of this. Figure 3 depicts the proposed CNN Architecture, which includes four layers of 3 x 3 matrices, two 2X2 max pooling layers, and a fully linked layer.

Dataset for proposed model

There are a slew of tomato illnesses that are wreaking havoc on the crop's leaves. Tomato disease images were obtained from the Kaggle database [7].More than 10,000 photos from over ten different tomato leaf variants are included in the dataset, including Mosaic virus, Target Spot, Bacterial spot, Yellow Leaf Curl

Virus, Late blight, Leaf Mold, Early blight, Spidermites Two-spotted spider mite, Healthy, and Septoria leaf spot. The experimental findings were assessed after these datasets were trained using the VGG 16 model, ResNet-50 model, and suggested CNN model.

EXPERIMENTAL RESULTS AND DISCUSSIONS

Throughout the development process, we used Google Colab, which was linked to my Google account [8].VGG 16, Resnet 50, and suggested CNN models were used to train the datasets. The photos were divided into three datasets: training, validation, and test, with split ratios of 70%, 15%, and 15%, respectively.9 distinct tomato leaf illnesses that typically occur in cultivations are trained on a healthy tomato leaf. The suggested CNN model is a deep neural network constructed with Keras sequential model and Tensor Flow backend support.

For processing the hidden and output layers, this model employed RMS prop as an optimizer, Image Data Generator as an input image pre-processor, Rectified Linear Activation Unit (ReLU), and Softmax. The input image is scaled to a predetermined size (150, 150, 3) and the model is divided into four layers, with the first and second layers containing 64 neurons and the remaining two layers containing 128 neurons. The loss of binary cross entropy (BCE) is calculated using this formula.

$$BCE = -\sum_{n=i}^{c} t_i \log(f(s_i)) + (1 - t_i) \log(1 - f(s_i))$$

Where: Si - weights/inputs - in this case, activation function , T - target predictions, I - predictor class

The suggested model is run for 100 epochs with a validation accuracy of 0.94, and the loss is determined using the above formula, after which the prediction classification for the supplied input image is generated to identify the classification. The suggested CNN model's training and validation losses are shown in Figure 4.The training loss is 0.2191 and the validation loss is 59.7028, according to the graphical representation. Figure 5 shows the suggested CNN model's training and validation accuracy, from which it can be deduced that accuracies were improved to 0.9441 and 0.7146, respectively.

Testing is carried out after analysing the performance of the proposed model, for which approximately 1000 samples were taken for 10 different classes, and it was discovered that the testing accuracy ranges from 80% to 100% during the prediction process, with the proposed model's average accuracy being 94.63 percent. (A) Results of the proposed model versus pre-trained models: The comparison results of the proposed CNN model with the pre-trained Resnet-50 and VGG-16 models are shown in Table 1.All of these models share the same dataset, and classification identification is completed. The findings reveal that the suggested CNN model outperforms the other pre-trained models in terms of accuracy and loss. We also used the RMS prop optimizer to get the desired results.

The number of trainable and non-trainable parameters in the proposed and pre-trained models was compared, and the suggested model outperformed the pre-trained models by a wide margin. Figures 6 and 7 shows the accuracy loss in the proposed and pre-trained models in comparison bar charts.

CONCLUSION AND FUTURE SCOPE

In this study, the performance of pre-trained models for image classification is compared to a proposed model built with a Convolution Neural Network (CNN), and it is discovered that the proposed model outperforms the pre-trained models in terms of training parameters. It's also been discovered that the proposed CNN model's training and validation accuracy outperforms other pre-trained models in terms of testing and validation. As a result, it has been determined that the proposed model has a higher efficacy of classification of leave sickness. Furthermore, the recommended model, as chosen by the optimizer, produces superior classification results than the pre-trained models. Furthermore, this proposed approach can be utilised to successfully classify disease in any tropical plant. This concept can be developed and deployed as a commercially viable application interface that will benefit home gardeners.

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Table 1. dataset, and classification identification

Model Name	Total Parameter trained	Number of Trainable Parameter	Number of Non-Trainable Parameter	Optimizer	Accuracy	Loss
Pre-trained ResNet50	24,591,242	1,003,530	23,587,712	Adam	0.7563	0.5661
Pre-trained VGG-16	14,965,578	250,890	14,714,688	Adam	0.8677	0.3873
Proposed CNN	3,477,066	3,477,066	0	RMSprop	0.9463	0.2191

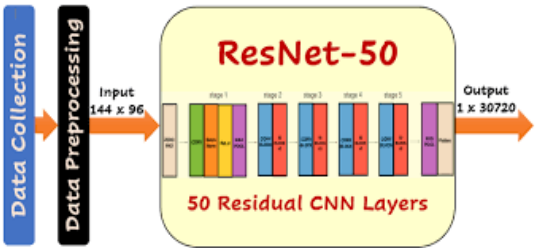

Figure 1 : Pictorial representation of the ResNet 50 Architecture

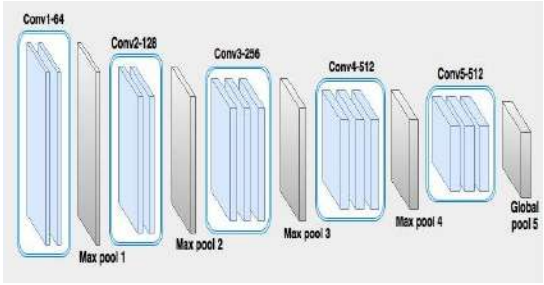

Figure 2: Pictorial representation of the VGG-16 Architecture.

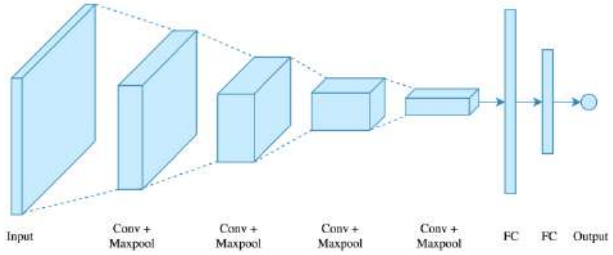

Figure 3: Pictorial representation of the Convolution Neural Network (CNN) Architecture

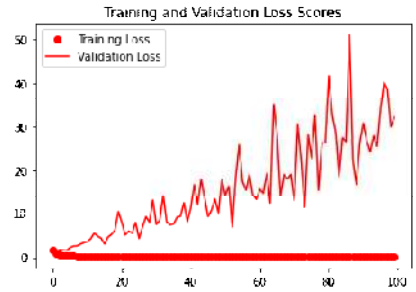

Figure 4: Training loss and Validation loss of proposed CNN model.

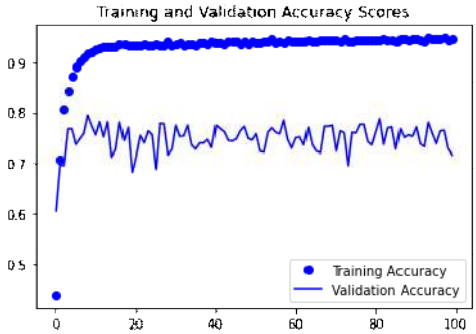

Figure 5: Training and Validation Accuracy of proposed CNN model

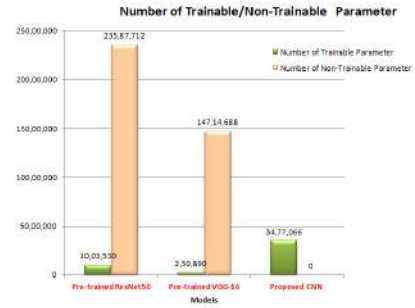

Figure 6: Comparison of number of trainable/Non-trainable parameters in various models

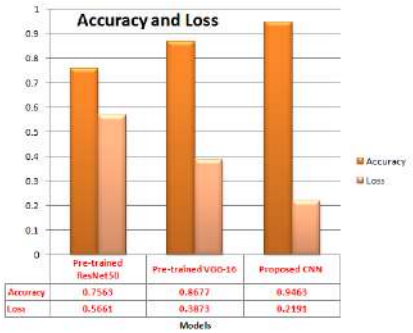

Figure 7: Comparison of accuracy and loss obtained through various models

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RESEARCH ARTICLE

Climate Conditions Analysis of Environmental Affects on Solar Panel Performance

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ABSTRACT

In this project presents a sun's radiation converted to electricity through photovoltaic module. The solar module efficiency relies on sun intensity. Solar energy is most readily available source of energy. It is non polluting and maintenance free. In this work, we present an experimental study of a particular photovoltaic panel. It is self-cooled due to its open design which facilitates external respiration helping to improve its performance mainly in hot hours of the day and to avoid dust hoarding on its surface. The solar panel is a passes solar radiation through switching circuit. That battery is connected to source side of energy meter and load side of inverter is connected to solar system. Main concept in this project is DC from the battery is converted into AC by inverter and it is given to the load. In the proposed system is main scientific goal of photovoltaic is to produce solar cells and solar systems with high efficiency and which are economically acceptable.

Keywords: solar panel; photo voltaic; inverter; solar radiation.

INTRODUCTION

The photovoltaic (PV) materials convert to luminous energy into electrical energy called "Photovoltaic effect". Solar cells or photovoltaic cells are electrically producing equipment made of Semiconductor materials like a silicon. In the photovoltaic cells are vary in sizes and shapes. A involved relationship between voltage and current is indicate by the P-N junction in the solar cell. Photovoltaic cells employ a solid state diode structure with a large area on silicon. The surface layer very thin and then transparent. So that light can reach the junction region of silicon polymer. The solar cells are building blocks of photovoltaic modules. It is a device that electrical characteristics such as current, voltage or resistance vary when exposed to light. A solar panel or module is a series of interconnected silicon cells and it is joined together to form a circuit. The size of an array and the type of the module depends upon the amount of sun light available in a particular location and the climate conditions. In the solar energy can be made use of two ways the thermal route using for dying, heating, cooking or generation of electricity or through the photovoltaic route which converts solar energy into electricity that can be used for a various purpose such as lighting, pumping and generation of electricity. To estimate power from the solar modules, a suitable model required. The solar photovoltaic is a main component of solar power plant system. A charge controller is used to prevent overcharging and prevent against overcharging. It is a frustrate from completely draining a battery.

Solar Pv System

The solar photovoltaic (PV) system is a renewable energy technology which the transforms the energy from the sun radiation into electricity using photovoltaics. These photovoltaic's, also known as solar panels, provide a reliable green energy solution. A solar PV system is a sustainable, low maintenance option for anyone who wants to contribute to a greener environment, as the system does not cause any pollution or emissions and has numerous advantages. Photovoltaic systems use photovoltaic cells to collect solar energy from the sunlight, and converts it into direct current(DC) electricity. The reflection of the sunlight will create an electric field across photovoltaic systems, causing electricity to flow. The DC electricity will be transported to an inverter, which will convert this DC power into alternating current (AC). This AC power is the type of electricity which is used for the electric appliances in our domestic purpose, also referred to as AC load. The solar PV system is mainly three types of a grid-tied, grid or hybrid and off-grid. These, installation uses grid-tied inverter and does not have any battery storage. It is a simple to design and is very cost effective.

The grid tied system with battery back-up, otherwise known as a grid-hybrid system. Battery based grid-tied systems provide power during an outage and can storage energy for use in emergency. It is a use energy during peak demand times because can store the energy in the battery bank for later usage. In the off grid systems are great for a customer does not connect to the grid. Because in the geographical location or high cost of bringing in the power supply. It can be energy is self sufficient and can power remote places away from the grid in the photovoltaic cells.

Block Diagram

The solar panel is absorbs a solar radiation and produces electricity from the panel. The charge is given to the charge controller which keeps the charge in the system and it is a variable range and protecting the components from any transients. The controller charge is given to the battery bank and stored in the direct current(DC) then, the battery is converted a DC current into AC current by inverter and it is given to the load. In case of less voltage an optimizer is placed at the inverter output to check the output current. The solar panel is placed a geographical location and to energy utilized during a day time to under the climate conditions.

They work on the principle of the photovoltaic effect a based on the solar cells or photovoltaic cells are made. They convert sunlight into direct current to electricity. But, a single photovoltaic cell does not produce

enough amount of electricity. The overwhelming majority of solar cells are fabricated from amorphous (non crystalline) to poly crystalline to single crystal silicon forms.

A solar cells can be arranged into large groupings called arrays. These arrays, composed of many thousands of individual cells, can function as central electric power stations, converting sunlight into electricity energy for distribution to industrial, commercial, and residential users. Solar cell panels are used toprovide electric power in many remote terrestrial locations where conventional electric power sources are prohibitively expensive to install. A solar cell is installations from communications and weather satellites to space stations. Solar energy is very convenient to use during summer season when the sun rays are very strong and it is a lot of solar energy can be generated. According to manufacture standards, a 25º c temperature indicates the peak of the optimum temperature range of solar panels and it is various weather conditions.

Climate Condition Analysis

An analysis of the solar irradiance, temperature and humidity of solar panel is presented. The analysis of located weather data patterns shows that solar power, wind power and temperature can remittance well for one another, and can enhance computable utilization factor for renewable energy applications. In the climate conditions of Namakkal district based on height about sea level is 882m. the maximum air temperature is 30ºc and maximum temperature is 15ºc. the relative humidity of Namakkal at maximum is 95.1% which is during monsoon and minimum is 18.3% of under the climate conditions. The place of installation is Paavai engineering collage and the latitude is 15* and longitude of the place is 85*, all the allotted land area is 190 feet. The nominal capacity of the power plant is 3.5kw. the solar PV plant has 14 modules and the solar cell material made by polycrystalline and modules are inclined at 15 degrees, 250wp used for series and parallel.

Solar Panel Performance

One way of exploit the energy of the sun is to generate electricity directly from the sun light by the photo voltaic process. The photo voltaic effect is defined as the engendering of an electromotive force as result of absorption of ionizing radiation. Energy conversion devices which are used to convert sun light to electricity by use of the photo voltaic effect are called solar cells. The photo voltaic effects can be perceive in nature in a variation of materials that have shown the best performance in sunlight is the semiconductors. When the non particulate radiation from the sun is absorbed in a semi conductor, they create free electrons with higher energies than the electrons which provide the bonding in the base crystal. The electric field in most solar cells is provided by a junction of material which has different electrical properties. Photovoltaic conversion of solar energy involves a wide range of knowledge as a energy problems, properties of solar radiation reaching the earth's surface, photovoltaic effect in the p-n junction, properties of semiconductors which are important in photovoltaic conversion, technology of solar cells, construction of solar panels modules and arrays, control systems of photovoltaic power station as well as ecological and economical problems of photovoltaic installations.

The photovoltaic effect can be described as a generation of electromotive force (voltage) within the wide range of material to non homogeneity during light illumination with an appropriate wave length. The solar module is the uses of electronic characteristics of semiconductor materials to achieve solid PV conversion device, in the off-grid areas, the device can be easily implemented as user powered lighting and living, an some developed countries also regional power grid to achieve complementarities. The charge controller of a solar power system to be a over-charging protection, short-circuit protection, pole confusion protection and automatic dump- load function. It is also function is vary the power as per the load demand. The controller disconnects the battery bank from array when the battery is fully charged and also cuts off the load when the battery is discharged a specified level. A inverter can produce square wave, modified sine wave, pulsed sine wave, or sine wave depending on circuit design. It is a two basic designs for producing household plug in voltage from a lower DC source, the switching boost converter to produce a higher voltage in the system.

An inverter is an electronic device capable of transforming a DC current into an alternating current (AC) at a given voltage and frequency of a solar power plant.

CONCLUSION

In this project solar power generation system is good and effective solution for power generation than conventional energy resources. A solar power in different radiation measurement during a various climate conditions.Determine the power through light radiation fall on the earth surface.

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RESEARCH ARTICLE

Root Morphology in Pulses Specially Gram

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ABSTRACT

In the arid lower River, insufficient water resources limit the growth and survival of planted seedlings of agriculture, which is critical for the rehabilitation of Cultivation and Non-Cultivation Areas.The goal of this study was to compare root morphology and biomass production of seedlings treated with two irrigation methods, namely side deep-ditch irrigation and above-ground irrigation, as well as three water levels, namely high water level once, medium water level twice, and low water level once.

Keywords :- Irrigation ,Morphology, Root, Seedlings.

INTRODUCTION

Plant growth regulators are chemical compounds that control the growth and differentiation of plant cells, tissues, and organs at low concentrations. To put it another way, they are chemical messengers that allow cells to communicate with one another. Biochemicals produced by plants (endogenous) or synthetic compounds given to plants (exogenous) are examples of these. These are used to reduce vegetative growth, enhance photosynthetic efficiency, improve the source-sink relationship, and improve fruit retention.

Pulse Root Cropping System

Due to its rotational benefits and possible profit margins, pulses are a major component of crop production systems in Southern India. Low soil water availability and subsoil restrictions, on the other hand, hinder agriculture in temperate agricultural systems like those of Southern india. This shortage of soil water is exacerbated by the inconsistency of rainfall, resulting in a lack of plant-available water at depth. Increased productivity of major pulses,

as well as expansion into settings and soil types formerly deemed problematic for their growth, would necessitate more efficient use of limited soil water and adaptation to sub-soil constraints. Roots act as a link between the earth and the rest of the plant. Root system architecture (RSA) changes can be used as an adaptive method for maximising yield potential in the face of limited rainfall, heterogeneous resource distribution, and other soil-based restrictions. A "'Steep, Deep, and Cheap" root ideo ztype has been discovered as a favoured RSA in the literature. In a temperate system, however, where plant accessible water is limited at depth, this ideotype is ineffective. Furthermore, due to their monocotyledonous origin and detachment from pulses, this root ideo type and other root architectural research have focused on cereal crops, which have different structures and growth patterns than pulses. Because there are few pulse-specific root architecture studies, more research on pulse RSA is needed, as well as an examination of the current variability of known genetic features, in order to develop strategies to alleviate production limits through tolerance or avoidance mechanisms. In temperate cropping systems, this paper presents a new model of root system design based on pulse roots for "Wide, Shallow, and Fine" roots. In addition to other root features, the suggested ideotype has a root density concentrated in the higher soil layers to capture in-season rainfall before it evaporates.The research points out that essential pulse crops like chickpea, lentil, faba bean, field pea, and lupin have the capacity to achieve this. Comparisons to determinate crops such as cereals have been made where possible. The analysis outlines significant root features that have exhibited a degree of adaptation to water stress via tolerance or avoidance, as well as the existing known variability in and among pulse crops, establishing research objectives.

The timing of factors affecting yield and yield components matched the present understanding of pulse root phenology. The days to maturity of pulse crops vary based on temperature, photoperiod, and rainfall after sowing. From maturity, the reproductive and ripening phase might extend anywhere from 30 to 35 days. Plant emergence, which is dependent on adequate taproot growth and establishment, is the first factor in crop production following sowing. At the early seedling stage, the first-order lateral roots (LR) form after the taproot. Early vigour is crucial for biomass build-up and harvest index at the seedling stage. Roots spread rapidly from seedling to flowering, expanding deeper into the earth and densifying as higher-order laterals emerge. Root growth aids nutrient and water uptake, resulting in an increase in the number of successful blooms that mature into seeds. Soil moisture levels can be drastically lowered during pod filling, and pulses' root flush potential may allow the final rush of root development to extract more soil moisture.

Root System Morphology

The crops that are widely produced in the semi-arid tropics (SAT) face nutrient and water scarcity.The shape and physiology of the root system are important factors in crop species' mineral and water intake, especially under stress, and thus impact biomass output and crop yield. In order to exploit limited soil resources, a well-developed root system is required for crop establishment throughout the early stages of growth. A root system's ability to sustain crop growth is largely determined by its architectural structure and uptake ability. Our earlier research looked at the kinetics of nitrogen uptake in the presence of low and high nitrogen availability. The genetic enhancement of any crop cultivated under adverse conditions requires morphological and physiological characterisation of the root system. The results of this research can be used as input parameters for a nutrient uptake model, which is an important part of the crop growth model. It's also valuable for understanding the competition between roots for soil nutrients when crops are grown in intercropping systems.

Root system variation of pulse crops

The direct extension of the radical in the majority of dicotyledonous plants results in the creation of a primary root that grows inside the soil. It has lateral roots of several orders, known to as secondary, tertiary, and so on. The tap root system, as shown in the mustard plant, is made up of the major roots and their branches The primary root of monocotyledonous plants is short-lived and is replaced by a vast number of roots. As shown in the wheat plant, these roots grow from the base of the stem and form the fibrous root system. . Adventitious roots emerge from portions of the plant other than the radicle in some plants, such as grass, Monstera, and the banyan tree. Absorption of water and nutrients from the soil, appropriate anchorage of plant parts, storage of reserve food material, and

synthesis of plant growth regulators are the key tasks of the root system. Pulses, The word "pulse" comes from the Latin words "puls" or "pultis," which imply "thick soup."Pulses are edible seeds collected from the fruits of the Fabaceae family. They give people all throughout the world with a crucial supply of plant-based protein, vitamins, and minerals. Gramme of black *Vigna mungo* is the botanical name for this plant. Black gramme is indigenous to India and is grown there. Black gramme was first discovered roughly 3,500 years ago, according to archeobotanical evidence. In the drier portions of India, it is grown as a rain-fed crop. India is responsible for 80% of the world's black gramme production. In India, the states of Uttar Pradesh, Chattisgarh, and Karnataka are important producers of black gramme. Uses Whole or split black gramme, boiled or roasted, or crushed into flour are all options. In the creation of popular Southern Indian morning dishes, black gramme batter is a key ingredient. Indian curries are seasoned with split pulse. Pigeon pea / Red Gram *Cajanus cajan* is the botanical name for this plant.

Origin and Area of cultivation

It is Southern India's only native pulse. Maharashtra, Andhra Pradesh, Madhya Pradesh, Karnataka, and Gujarat are the primary producers. Uses Red gramme is a key ingredient in sambar, a popular Southern Indian meal. Roasted seeds are a popular snack that can be eaten salted or unsalted. The young pods are fried and eaten. Gramme of green *Vigna radiata* is the botanical name for this plant. Origin and Cultivation Area Green gramme is an Indian native, with the earliest archaeological evidence dating back to Maharashtra. Madhya Pradesh, Karnataka, and Tamil Nadu are the states where it is grown. It's a roasted, cooked, and sprouted pulse that can be utilised in a variety of ways. It is the only native pulse of Southern India. The primary producers are Maharashtra, Andhra Pradesh, Madhya Pradesh, Karnataka, and Gujarat. Uses In sambar, a classic Southern Indian dish, red grame is a vital component. Roasted seeds, which can be salted or unsalted, are a popular snack. Young pods are fried and consumed. Green grammage This plant's botanical name is *Vigna radiata.* Area of Origin and Cultivation Green gramme is a native of India, with the earliest evidence dating back to Maharashtra. It is grown in the states of Madhya Pradesh, Karnataka, and Tamil Nadu. It's a roasted, cooked, and sprouted pulse with a wide range of applications. Chickpea seed flour is a key ingredient in a variety of Indian sweets. Whole or split gramme, roasted and salted, is a favourite middle-class snack.

Morphology

(Morphe = form + logos = research)It is concerned with the study of the forms and characteristics of various plant organs such as roots, stems, leaves, flowers, seeds, and fruits. A typical angiospermic plant's anatomy is divided into two parts: a subterranean root system and an aerial shoot system. The stem (including branches), leaves, flowers, and fruits make up the shoot system. The vegetative portions are the roots, stems, and leaves, whereas the reproductive parts are the flowers.

Plants

Annual plants complete their life cycle in a single year, growing season, or a few weeks to a few months. They survive the unfavourable era as seeds, such as mustard and pea. Biennials — They have a two-year life cycle, with the first year being spent growing, vegetative, and storing food, and the second year being spent blooming and fruiting. After generating flowers and fruits, they die off, for example. In cooler climates, radish, turnip, and carrot are biennial. In warmer climates, they become yearly. Perennials are plants that live for numerous years. Flowers and fruits are produced every year by these plants, and they do not die after flowering. Radicles emerge from the seed coat in the shape of a soft structure and travel toward the soil, as in mango, banana, and guava. It grows and develops into a major root.

General Characters:

Roots are non green, underground, (+) geotropic, (–) phototropic and (+) hydrotropic.
Roots do not bear buds.
Buds present for vegetative propagation in sweet potato (Ipomea) and Indian red wood (Dalbergia)
Roots do not bear nodes and internodes.

Roots have unicellular root hairs.
Roots are of two types :
Roots are non-green, underground, (+) geotropic, (–) phototropic, and (+) hydrotropic in nature.
Buds do not grow on roots. Sweet potato (*Ipomea*) and Indian red wood both have buds for vegetative proliferation (Dalbergia) Nodes and internodes are not seen in roots.
Roots have root hairs that are unicellular.
There are two sorts of roots:

Tap root
It grows from a radicle and consists of one major branch and several smaller branches. Tap root system is made up of primary roots and their branches. Dicot roots, for example. Adventitious roots: In some plants, the growth of the tap root that emerges from the radicle ends after a period of time, and subsequently roots emerge from other parts of the plant, which are branching or unbranched, fibrous or store, and form the fibrous root system.
Monocot roots, for example.

Two Adjacent Plants Root
In the short term, new tools like partially resistant cultivars and pathogen avoidance based on individual field risk assessments will be critical additions to existing tools like seed treatment and early, shallow seeding to manage root rot risk and maintain or even increase pulse production across the region. Root lodging is known to lower maize yield and quality, and changes in agriculture such as increasing planting density and more intense precipitation events would exacerbate the problem.

We describe a new maize farming strategy that reduces root lodging. In a hole with the same density, we devised two planting layouts: twin plants (TP) and single plants (SP).Between two planting schemes, vertical root-pulling resistance, angle and rate of natural root lodging, root and shoot morphology related to root lodging, and maize yield were compared. The vertical root-pulling resistance and angle of natural root lodging were both greatly increased by TP planting. This is due in part to the gripping force between the two nearby plants' staggered crown roots. Furthermore, by raising the root angle (acute angle between the stem direction and the root) and stem diameter, TP planting could boost root-lodging resistance. Furthermore, TP planting had no effect on maize yield or biomass. As a result, our research found that twin plants in a hole are efficient in reducing maize root lodging in the southwest. This technology is easy, inexpensive, safe, and reliable, and it has the potential to increase maize output and quality in a wider range of situations. The gripping force between the staggered crown roots of the two adjacent plants considerably boosted the vertical root-pulling resistance of maize when twin plants were laid out in wide-narrow rows.

CONCLUSION

The study indicated that planting twin plants in wide-narrow rows arrangement (TP) can greatly boost maize vertical root-pulling resistance and angle of natural root lodging at our test location. This could be due to the gripping force between the crown roots of the two plants next to it. Additionally, TP planting enhanced root angle (acute angle between stem direction and root) and stem diameter, both of which were associated to root-lodging resistance. Furthermore, TP had no effect on maize yield. As a result of our research, we were able to develop an effective and acceptable planting approach for controlling root lodging in maize in southwest. Furthermore, as compared to other root lodging prevention strategies, TP planting scheme is simple, low cost, safe, and stable. As a result, this strategy will be useful in a changing agriculture that increases the risk of root lodging on maize, and it may be useful in facilitating the use of double plants.

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RESEARCH ARTICLE

Teaching and Learning Research on the Application of Artificial Intelligence and Cloud Computing

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ABSTRACT

This paper proposes an online intelligent form filling system based on an Excel template, in which users can upload a spreadsheet, share it to friends or other users to fill out, and then summarise all the filled spreadsheets. This technology overcomes time and space limitations during form filling by automatically extracting essential information from history filling data, reducing the effort of form filling and aggregation. The system's main technology is detailed, as well as the design and development process. The classic e-learning approach has been widely employed in the learning environment for several years. The rapid advancement of technology, such as the expansion of the Internet, has aided in the evolution of the learning environment. Institutions have studied how to improve learning by implementing modern learning and teaching infrastructure [1].This is one of the reasons why cloud-based e-learning is becoming more popular among educational organisations. A large number of students have praised the growth of cloud-based e-learning and predicted that it will be the way of the future in education

Keywords: Cloud-based e-learning, Google Sheets , Virtual Learning Environment

INTRODUCTION

The cloud-based e-learning paradigm was introduced to overcome the challenges of the traditional e-learning model in terms of resource utilisation and allowing learners to access learning material from any location [2].Because of the advancement of technology, institutions who take the initiative to integrate cloud services are expected to gain from lower operating costs and improved service delivery [1].As a result of the benefits it delivers in an electronic learning

environment, cloud-based e-learning has been progressively gaining traction[3]. Institutions like to work with a model that gives benefits while also being cost reasonable to maintain. The conventional model was expensive to maintain, and several of the features required modifications to work. It is true that upgrading more than half of a facility's computers is costly[1].A good online learning interactive system in real time can be provided by using a Google classroom and Google Sheets , Forms , Quiz as an E-learning platform. Both students and teachers can benefit from the Google classroom learning environment's extensive shared resource storage. The major goal of this project is to investigate and quantify the characteristics that influence student acceptance of Google classrooms in college.

Education

Human civilization entered the digital age as a result of the 4.0 revolution. In this situation, technology serves as a tool for humans to perform jobs and function more efficiently. This is a problem that also affects pupils. The ease with which kids can acquire information via the internet has both beneficial and harmful consequences. They might actively look for information sources that are pertinent to their college tasks. However, because of the volume of data obtained, they are less picky in their source selection. Based on the (WSIS) Declaration, which asserts that anybody can generate access, utilise, and exchange information and knowledge, everyone must be able to appropriately confront and master information. With the rapid advancement of information technology and the widespread adoption of the internet, office automation is maturing. By combining modern science and technology with the use of information resources, we have substantially increased the efficiency of our work and achieved excellent outcomes. Filling out a form, while a regular action in normal work, can be a time consuming process that reduces workplace efficiency. To begin, the manager must distribute forms to all users and then summarise all of the forms once they have been filled out and gathered. This procedure could take 3-4 days or perhaps a week to complete. Second, some fields in the form, such as name, gender, phone number, and email address, may be the same or identical to those in prior forms. Finally, the contents filled out by users may be diverse, resulting in data integrity issues. Google has launched online office software against Microsoft Office since 2010, such as "Writely" and "Spreadsheet," in order to expand the application domain of office automation and achieve mobile office or remote office, and Microsoft has also officially launched the online version of the Web Office 2010.Additionally, certain methods [1-3] have been proposed for auto-filling or auto-completion of web forms. All of the efforts are worthwhile, but they will not be enough to overcome the aforementioned flaws, particularly in terms of data integrity.As a result, we created an online intelligent form filling system based on an Excel template or word template.

Design and Analysis of Systems

System Modules (A)There are two types of users in this system: common users and system administrators. Users can upload Excel template files with bespoke formats, which will be parsed and generated into relevant web forms automatically. The web forms can then be filled up by authorised users (such as their friends) and a statistical analysis run. System managers keep an eye on the system to make sure it's working smoothly and accurately. As shown in Figure 1, this system has five modules: template management, form management, friend management, user management, and system management.

System Modules (A)

There are two types of users in this system: common users and system administrators. Users can upload Excel template files with bespoke formats, which will be parsed and generated into relevant web forms automatically. The web forms can then be filled up by authorised users (such as their friends) and a statistical analysis run. System managers keep an eye on the system to make sure it's working smoothly and accurately. As shown in Figure 1, this system has five modules: template management, form management, friend management, user management, and system management.

Managing Your Friends

This module is mostly used to keep track of a user's friends. Common users can permit all users to fill out web forms in this system, or they can only designate for parts of their friends. Management of users. This module is mostly used to manage the system's users. It also gives all users the ability to change their passwords. System administration. This module is primarily responsible for managing system data such as system settings, system codes, and fundamental data. In addition, data backup is included in this module.

The system's framework is depicted in Figure 2.The data centre, which consists of Excel template files and a database, is the bottom layer, where user information, template information, form information, and friend information are physically stored. Instead of connecting directly from applications, mechanisms to access the data centre are contained inside data share interfaces or agents in the data access layer. The business logic layer is a crucial layer that implements the above-mentioned system components' business procedures. The user interface is built as a presentation layer that only accepts user input and displays the results from the business logic layer, which executes transactions based on the top layer's parameters. This system also includes centralised security administration and monitoring capabilities.

Parsing Templates

We define custom format symbols to present properties (such as control type, data type, and attributions) for each field in the spreadsheet to ensure the normalisation, validity, and integrality of the filled data when converting a spreadsheet with Excel template format into a corresponding web form. The custom format symbols are shown in Table 1. Fig 3 Google Classroom is a free Software as a Service programme developed by Google. It's a cloud computing service of some sort. Virtual Learning Environment is another name for Google Classroom (VLE).It is well-known for its use as a learning aid in higher education institutions. It offers two application platforms, Desktop and App application, which students and teachers can download for free from the Apple Store and Store, respectively, for IOS and Android operating systems. Fig 4 Google Docs is an online word processor that is part of Google's free, web-based Google Docs Editors suite, which also includes Google Sheets and Google Slides.

Creating a Web Form

Each field is created into an appropriate control while parsing the template, and then attached to a "Place Holder" control in the web form. According to its data attributions, the field may also be necessary to connect a validation control, which allows us to simply and automatically validate the input value.

Information Retrieval and Matching

Users frequently fill out a variety of forms in the workplace, and many of the fields in these forms are highly repetitive, which can be optimised by intelligently reusing the user's data.As a result, we use clever technology to match and retrieve information that the user has already filled out.Three circumstances that may arise during information matching and extraction are listed below: In each form, the system will directly pull information from previously filled out areas with the same name, such as "Name" and "Gender."If the user filled out different information, the system will extract the information from the most recent filling and display a list of all information ever completed for the user to choose from. For example, if someone has previously filled out "music" in the "Hobby" area through our system, the system will now automatically fill out "music" in the "Hobby" field for him. If he changes the information to "game" at this point, the system will again fill in "game" and present a list that includes "game" and "music."

Users can create a synonym table in preparation for fields with the same meaning but different names (such as "Gender" and "Sex"), and the system will match the synonym of the field name and fill out the field according to the former criteria. • For variables with a computational link (such as "Age" and "Date of birth," or "Amount," "Unit Price," and "Quantity"), users can create a formula table or a formula expression for this field in the Excel template, and the system will calculate the outcome.

CONCLUSION

This paper proposes an online intelligent form filling system, outlines the system's modules and framework, and discusses three important technologies. We can break through time and space boundaries during form filling with the help of this technology, reducing the workload of form filling and aggregation, and therefore improving the efficiency of our work. We'll concentrate our efforts on conducting more in-depth study on template parsing in order to accommodate more document formats, such as Microsoft Word and editable PDF.We will also continue to investigate semantic matching technologies in order to improve the intelligent level of information matching and extraction. To summarise the primary research issues and their solutions, the old e-learning paradigm is no longer appropriate due to advancements in technology that provide free-of-charge and low-up-front requirements, as we described above. The widespread availability of technology, a large number of strong rivals in the market, and an IT-skilled generation have all aided the acceptance of e-learning in education, regardless of the learners' and instructors' geographical locations. The cloud-based e-learning model has filled a vacuum in the traditional e-learning model in terms of risks and security issues, as cloud-based e-learning services will give a service with SLA, and security is one of such service provider's key priorities. Finally, institutions must choose the appropriate approach to cloud computing services depending on their needs in order to get the results they want from cloud-based e-learning.

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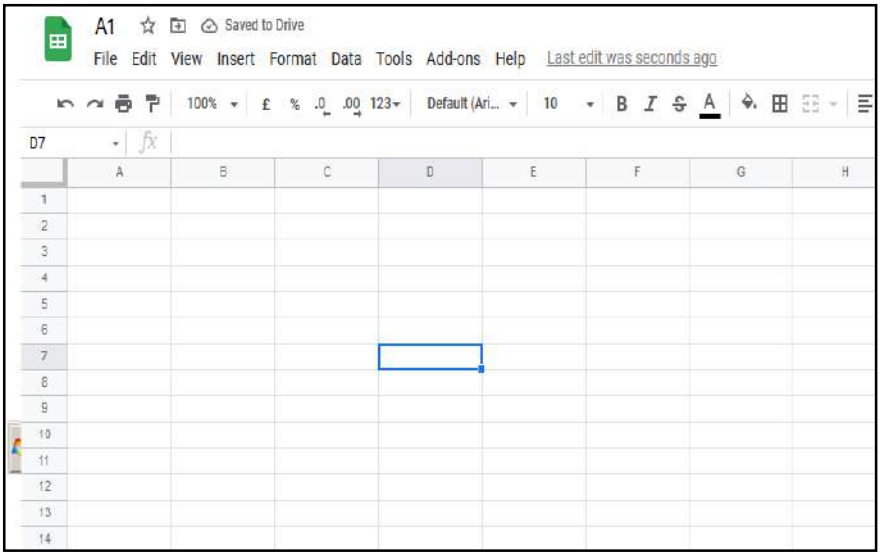

Table 1. Parsing Templates

Fig.1. Google classroom

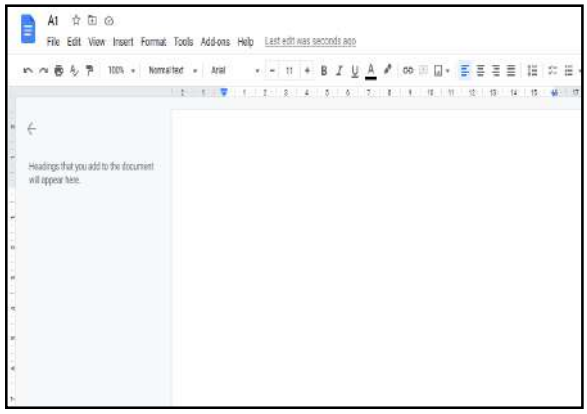

Fig. 2. Online Google Docs

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RESEARCH ARTICLE

Antioxidant and Anti-Obesity Potential of Selected Herbs

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ABSTRACT

Plants have been widely studied as lead compounds for pharmacological products. They have many constituent secondary metabolites that impart useful medicinal properties. These secondary metabolites often contribute to the presence of anti-oxidant properties in the plants. Anti-oxidant property is known to counter many lifestyle diseases as diabetes, cardiovascular diseases, cancer, aging etc through free radical scavenging activity .Many plants & herbs have been used in traditional systems of medicine and household remedies since the ancient times. However the principle behind their action is being studied in recent times. The anti-oxidant activity of many plant species and their action against the reactive oxygen species are being explored and characterized.

Keywords: Anti-oxidant, DPPH ,Plants, Herbs.

INTRODUCTION

With increasing research in the area of natural anti-oxidants, many novel sources such as plants, plant products like fruits and microorganisms are being discovered that can aid in the development of natural anti-oxidants to replace the synthetic ones. Similar to the anti-oxidant property, secondary metabolites also confer other useful medicinal properties; such as natural enzyme inhibitors. Obesity is another important lifestyle disease for which new treatment modalities are being developed. Obesity is a health issue of the global level with 500 million adults affected. It is garnering interest as there are no permanent and natural management options. Thus now phytochemicals are being studied for viable options.

One possible anti-obesity treatment is that of Pancreatic Lipase Inhibitor. Pancreatic Lipase is the enzyme responsible for the digestion of triglycerides. When this is inhibited, the dietary triglycerides absorption is reduced thus reducing the calories .This treatment is now gaining popularity as it does not interfere with any other physiological function

(Shi and Burn,2004). If the lipase inhibitor is obtaining through a natural source it also greatly reduces the adverse effects of chemicals. Thus examination and validation of anti-obesity activity of photochemical will lead to the development of novel efficient dietary supplements to counter obesity.

MATERIALS AND METHODS

Sample Collection

To evaluate the anti oxidant and anti-obesity by pancreatic lipase inhibition of herbal extracts ten different plant samples were randomly selected and their potential was determined under laboratory conditions.

Sample Preparation And Extraction

The herbal plants were purchased from Anna siddha hospital, Anna Nagar, Chennai. The samples were shade dried for a week of time and grounded using mortar and pestle. The powdered samples were kept in airtight containers for further study. Twenty five grams of the samples were taken individually and was extracted with 300 milliliter of ethanol using Soxhlet apparatus for ten hours of time. After each extraction the extractant was collected from the apparatus and condensed the same using rotary evaporator at 50°C under reduced pressure. The resulting crude extract was made to a concentration of 100mg/ml with ethanol and stored in a refrigerator.

Antioxidant Assay

DPPH Assay

The assay was determined as described by Molyneux (2004).A clean test tubes were arranged as a row and labeled properly as that of concentration and as blank.3.7 ml of methanol was added in all the tubes. 100µl of sample was taken at each concentration (200 µg/ml, 400 µg/ml, 600 µg/ml, 800 µg/ml and 1000 µg/ml) and were added to the labeled tubes. 100µl of molecular grade water was added to the blank tube .Then all the tubes were incubated at room temperature for 30 minutes. After incubation absorbance was read at 517nm and recorded.

$$\% \text{ Antioxidant activity} = \frac{\text{Absorbance of Blank} - \text{Absorbance of Test}}{\text{Absorbance of Blank}} \times 100$$

Ferric Ion Reduction Potential (FRAP)

The assay was determined as described by Benzie and Strain(1996). Distilled water of volume 1ml was taken and 80µl of all the ethanol extractsat concentrations 200 µg/ml, 400 µg/ml, 600 µg/ml, 800 µg/ml and 1000 µg/ml were pipetted out respectively one by one into the standard 4ml plastic cuvette. Then, 600µl of incubated FRAP Reagent was added to the cuvette and it was briefly inverted to mix the solutions. The reagent blank was also prepared as described above but 80µl of distilled water was added instead of extracts. The change in absorbance at 593 nm was recorded exactly at the fourth minute using spectrophotometer (Benzie and Strain, 1996).

FRAP value of sample (µM)= (Change in absorbance of sample from 0 to 4 minute/change in absorbance of standard from 0 to 4 minutes)x FRAP value of standard (1000µM)

Pancreatic Lipase Inhibitory Activity: (Chedda *et al*.,2016)

Reagents Required

- Para-nitrophenlybutyrate (PNPB)
- Porcine pancreatic lipase
- Sodium dihydrogen Phosphate
- Disodium hydrogen phosphate
- Triton –X- 100
- Acetonitrile
- Orlistat

All the reagents were purchased from SRL, SD fine chemicals.
Porcine pancreatic lipase and the standard Orlistat was purchased from Sigma-Aldrich**.**

Reagent preparation

Buffer Preparation

A: 100mM PBS – Dissolve 0.78 grams of sodium dihydrogen phosphate and 0.88 grams of disodium hydrogen phosphate in 50 ml of distilled water.
B: 150mM NaCl – Dissolve 0.43 grams of sodium chloride in 50 ml of distilled water. Then mix the A and B solution together.
C: Triton-X-100: 0.5% (v/v) - 0.5 ml of Triton –X 100 was added to the beaker containing the solution A and B.

Enzyme Preparation

The 6 milligram of porcine pancreatic lipase was dissolved in 10 ml of buffer solution and mixed well. The enzyme should be prepared as fresh before the analysis.

Working Solution

PNPB (p-Nitrophenylbutyrate) was used as the substrate. The working solution was prepared by dissolving 8.403 µl of PNPB in 10 ml of acetonitrile solution.

Procedure

Twenty five microlitre of the test samples and the standard was incubated with 50µl of enzyme solution. 100µl of buffer solution and 25 µl of PNPB were added to the same test tubes and was incubated for 30 minutes at 37°C.The activity was determined by measuring the hydrolysis of PNPB to p-nitrophenol at 400 nm using spectrophotometer.
%Inhibition = [(Absorbance of Blank-Absorbance of test)/Absorbance of Blank] x 100

RESULTS AND DISCUSSION

Antioxidant Activity of selected plants:

DPPH

The herbal plants selected in the present study exhibited profound antioxidant activity. The percentage inhibition of DPPH recorded in *C. quadrangularis* was43.76%.Rebecca et al., (2013) observed a lower level of(29.4%)activity with the same plant. Ali et al., (2018) studied the antioxidant potential of*C. Dactylon* and reported 68.17% in the ethanolic extract.The present study recorded highest inhibition (90.80%) in the ethanolic extract .Tohma And Gulcin,(2015)revealedthe antioxidant activity of *Glycyrrhiza glabra* by DPPHmethod**(**54.4% at 30µg/ml).but lower level of inhibition was recordedin the present study**(**36.25%).

FRAP

The ferrus reducing potential of the selected plants were found to be momentous. The ethanol extract of *Glycyrrhiza glabra* showed 1065 at the concentration of 1mg/ml. Rajinder et al., (2010) recorded slightly lower level (946)with the same concentration. Abedi ,et al .,(2017) studied the FRAP analysis in Nigella Sativa and confirms that the values were dose dependant. Further they reported higher values of antioxidant when compared to the present study. Abdulkedia et al.,(2016) reported the FRAP values of *Solanum torvum* methanolic extract of the fruits as 1120 .The ethanolic extract of the same exhibited slightly lower levels (940)in the present study.

Pancreatic Lipase Inhibitory Assay

Rana *et al*., (2018) screened about ninety crude plant extracts for their lipase inhibitory activity and reported that among the 90 herbal extracts examined 41% of the samples exhibited more than fifty percent inhibition. More significant results were recorded in the present study. All the ten samples tested were found to be significant

towards the pancreatic lipase inhibition. The widely used positive control Orlistat showed slightly higher percentage (95.454) than the previous study. Sharma *et al*., (2012) revealed that the methanolic fraction of *Camellia sinensis* possess significant inhibition towards the pancreatic lipase activity which exhibits the percentage inhibition of 86.2 at 1mg/ml concentration. They further concluded that the higher percentage was due to the presence of phytochemicals such as Carbohydrates, Alkaloids, Phenol, Flavonoids, Phytosterols and Saponins. In contrary to that significant results were obtained (89.359%) in the present study at a minimum concentration 25 µg/ml .

CONCLUSION

With more people avoiding chemical drugs for the management of overweight and obesity, due to the fear of health adverse side effects, tendency is now towards natural-based products; thus the development of new ant obesity molecules from natural products has become a necessity. Tis seems doable because, in traditional herbal medicine, several plants are used for their weight- reducing effects. The plant bioactive constituents are expected to act as natural inhibitors of digestive lipases Antioxidant and in vitro porcine pancreatic lipase, PPL, inhibitory tests were conducted on seventy-six plants, of which thirty-nine species with weight reducing or related potential were used in Palestinian traditional medicine, to find new crude antiobesity products from natural sources

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Table 1: Illustrates the plants and their parts selected for the study

S.NO	NAME OF THE PLANT(COMMON NAME)	SCIENTIFIC NAME OF THE PLANT	PARTS CHOOSEN FOR ANALYSIS
1	Pirandai/ Veldt grape/ Adamant creeper/ Devil's backbone	*Cissus quadrangularis*	Stem
2	Bermuda grass (Arugampul)	*Cynodondactylon*	Grass
3	Green tea	*Camellia sinensis*	Leaf
4	Bitter gourd	*Momordicacharantia*	Fruit
5	Turkey berry (Sundakkai)	*Solanum torvum*	Fruit
6	Black cumin	*Nigella sativa*	Seeds
7	Lemon	*Citrus limon*	Fruit
8	Liquorice (Athimathuram)	*Glycyrrhizaglabra*	Root
9	Yellow fruit nightshade (Kandankathiri)	*Solanum virginianum*	Fruit
10	Papaya	*Carica papaya*	Leaf

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RESEARCH ARTICLE

Information Systems Natural Language Processing: A Survey of Current Research Trends

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ABSTRACT

Text classification is one of NLP's many applications. The data for this study comes from the Automatic Speech Recognition (ASR) model, and it is used to construct a multi-label classification model for tagging plain text. The data gathering method, on the other hand, is carried out utilizing automatic speech recognition technologies (ASR). The project's main goal is to create an efficient model that correctly guesses the tags for plain text received with an accuracy of 84 percent. By examining all of them, it was discovered that supervised learning techniques such as Naive Byes and Support Vector Machine (SVM) performed better for Text Classification.

Keywords: NLP, ML, AI, Deep learning, chat bots

INTRODUCTION

Natural Language Processing (NLP) is in high demand in the era of knowledge, with a wide range of applications. Previously, NLP only dealt with data that was static. In today's world, NLP is doing a lot with corpora, lexicon databases, and pattern reformation. NLP tools grow increasingly precise and efficient as Deep Learning (DL) methods detect artificial Neural Networks (NN) as nonlinear processes, resulting in a debacle. The importance of the Multi-Layer Neural Network in NLP is increasing due to its capabilities, which include standard speed and resolute output. Data hierarchical designs operate recurrent processing layers to learn and manage many practices with this arrangement of DL approaches. This paper continues to strive for a review of the tools and essential methodology in order to offer a clear grasp of the relationship between NLP and DL in order to properly understand in the training. Part of speech tagging (POST), Morphological Analysis, Named Entity Recognition (NER), Semantic Role Labeling

(SRL), Syntactic Parsing, and Co reference resolution all help in NLP efficiency and execution. As a feature of Deep Learning, Artificial Neural Networks (ANN), Time Delay Neural Networks (TDNN), Recurrent Neural Networks (RNN), Convolution Neural Networks (CNN), and Long-Short-Term-Memory (LSTM) deal with Dense Vector (DV), Windows Approach (WA), and Multitask Learning (MTL). After statically methods, when DL communicated the influence of NLP, a basic relationship was established between the individual form of the NLP process and DL rule collaboration. Deep Learning (DL) is used to formulate Natural Language Processing (NLP) demand. Natural Language processing techniques, such as Artificial Neural Networks (NN) and non-linear processes, improve accuracy and efficiency, and DL rule collaboration was presented with the primary relationship. Text Classification and Categorization, Named Entity Recognition (NER), Part-of-Speech Tagging (POST), Semantic Parsing and Question Answering, Paraphrase Detection, Language Generation and Multi-document Summarization, Machine Translation, Speech Recognition, Character Recognition, Spell Checking, and other NLP tasks are all completely taken over by DL. When DL is present, NLP approaches are altered.NLP processes such as POS, NER, Morphology, Syntactic Parsing, and Co reference Resolution are linked to Neural Networks such as ANN, TDNN, RNN, and CNN. In addition, DL tools such as LSTM, MTL, DV, CBOW, VL, WA, SRL, and Non-Linear Function maintain a relationship with NLP processes to collaborate on basic relationships.

Natural Language Processing

Natural Language Processing (NLP) is a branch of science that helps computers understand human languages more naturally.NLP approaches' ultimate goal is to extract meaningful information from human languages. Human-Computer Interaction (HCI), on the other hand, is an interdisciplinary study area based on computer science, cognitive science, and human factors engineering principles.HCI is primarily concerned with how humans and computers interact with one another. A well-designed interface becomes an integral part of our daily lives, whereas a poorly built HCI causes unanticipated challenges. NLP techniques have had a wide range of applications in HCI over the last few decades, both theoretically and practically.NLP streamlines the human-machine interaction process while also improving user experiences. Natural language processing (NLP) has recently gotten a lot of press for its computational representation and analysis of human language. It has a wide range of uses, including machine translation and email spam detection. extraction of data, summarization, medical, and question answering, and so forth. The paper is divided into four sections, beginning with a discussion of different levels of NLP and components of Natural Language Generation (NLG), then moving on to the history and evolution of NLP, the state of the art, and current trends and difficulties. Natural Language Processing (NLP) is a branch of AI and linguistics concerned with making computers understand statements or words written in human languages. Natural language processing was created to make users' lives easier and to fulfill their desire to connect with computers in natural language. NLP caters to those users who do not have enough time to learn new languages or perfect them, as not all users are well-versed in machine particular language. A set of rules or a set of symbols can be used to define a language. Symbols are mixed and utilized to transmit or broadcast information. The Rules have a tyrannical grip on symbols. Natural Language Processing is divided into two parts: Natural Language Understanding and Natural Language Generation, which evolves the work of comprehending and producing text. Fig. 1 Linguistics is the study of language, and it encompasses Phonology (sound), Morphology (word formation), Syntax (sentence structure), Semantics (syntax), and Pragmatics (understanding).

Natural Language Generation (NLG)

Natural Language Generation (NLG) is the process of producing phrases, sentences and paragraphs that are meaningful from an internal representation. It is a part of Natural Language Processing and happens in four phases: identifying the goals, planning on how goals maybe achieved by evaluating the situation and available communicative sources and realizing the plans as a text .It is opposite to Understanding. Natural Language Processing (NLP) research at Google focuses on algorithms that apply at scale, across languages, and across domains. Our systems are used in numerous ways across Google, impacting user experience in search, mobile, apps, ads, translate and more. Natural language processing (NLP) is an artificial intelligence and computer science subfield that focuses on tokenizing and parsing human language into its constituent parts. NLP integrates computational

linguistics with statistical, machine learning, and deep learning models to allow computers to interpret human language in the form of text or speech data and fully comprehend its meaning, including the speaker's or writer's intent and sentiment. In fact, a typical Natural Language Processing interaction between humans and machines can look like this:

1. A human converses with a machine
2. The audio is captured by the machine.
3. Conversion of audio to text takes place.
4. Data processing for the text
5. The data is converted to audio.
6. In response to the human, the machine plays the audio file.

4.Purpose of Natural language processing

Natural Language Processing is at the heart of the following widely used applications:

- Word processors such as Microsoft Word and Grammar that use natural language processing to check grammatical accuracy of texts, such as Google Translate.
- In call centres, Interactive Voice Response (IVR) applications are utilized to answer to specific user demands.
- Voice-activated assistants such as OK Google, Siri, Cortana, and Alexa.
- We're seeing a machine–human synergy in various domains. Because a combination of computer analytics and human insight produces the best results, perhaps the sweet spot in qualitative analysis is a mix of machine learning and human analysis, in which we use NLP to speed up analysis and cross-check open coding while still relying on humans to critically evaluate the results.

CONCLUSION

NLP works through machine learning (ML). Machine learning systems store words and the ways they come together just like any other form of data. Phrases, sentences, and sometimes entire books are fed into ML engines where they’re processed using grammatical rules, people’s real-life linguistic habits, or both. The computer then uses this data to find patterns and extrapolate what comes next. The goal of this study is to look at how NLP can be used in the corporate world. The key to unlocking NLP's potential is to learn and understand natural language efficiently. It can deal with challenges like translation and transliteration by improving the communication process between humans and machines in a variety of formats. Based on the analysis, it can be stated that its use in various industry-based solutions has grown in recent years. Complex processes in business, such as stock market trading predictions and decision-making; streamlining client interactions with chat bots on commerce platforms, resulting in a more engaging encounter; In E-governance, analysing citizens' issues from enormous amounts of data; successfully managing healthcare operations, such as diagnoses, service delivery, and record keeping; NLP techniques can help with enhancing learning and teaching methods in the education industry, among other things. In addition, when NLP is combined with sophisticated technologies like machine learning, artificial intelligence, and deep learning, it can produce more accurate results than older approaches. However, its use in the fields of artificial intelligence, robotics, and other advanced systems is mostly unexplored. In conclusion, given the effectiveness of NLP techniques in improving the accuracy of data analysis and natural language processing, it offers enormous potential for future usage in robots and business intelligence.

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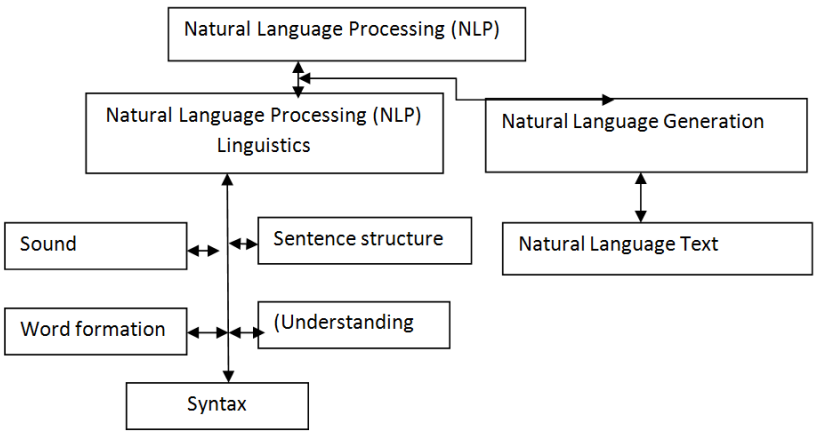

Fig 1 Natural Language Processing

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RESEARCH ARTICLE

Smart Ambulance System for Real Time Application

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ABSTRACT

Automatic system for ambulance is taking a prominent role in day to day life to save the critical stage patients such as severe injured due to road accident and severely affected by heart disease, etc. In this system, embedded, GPS and IOT technology are integrated for finding a shortest route and distance to reach the hospital or injured places. Live tracking and status information of all route, distance and traffic status of the possible path are provided to the ambulance driver which helps in acquiring right path to reach the hospital or particular places without any delay. GPS system is used to find the various route and distance of the hospitals. IOT systems are used to monitor the traffic of some important places such as jamming places and bridges, etc. GPS and IOT system are interfaced with Microcontroller. Based on traffic information, driver can change the route to reach the hospital very quickly. The audio voice will be provided in the moving path (Permanent audio installed jamming places) before moving to hospital and also gives to traffic police to make necessary action along the way. This system is very useful to save the people life which can be adopted for real time application.

Keywords: Embedded system, GSM, GPS and IoT Technology, Sensor.

INTRODUCTION

India is the second most population country in the worldwide and also growing country in all fields. Traffic jams are occurred in many cities and others places due to moving large vehicles. Intelligent management system can reduce traffic jams. In modern days, wireless networks are broadly used in the highway transport and provide more cost

effective options [1]. The Zig Bee, RFID, GPS and GSM can be used to control the traffic systems. The RFID is a wireless technology which is used in radio frequency electromagnetic energy to carry information between the RFID tag and RFID reader. The RFID systems will work in short range only such as inches or centimeters or meters. If reach to hospital within golden hour, the severely injured or heart disease patients can save the life. Smart Ambulance system is increases the likelihood of patients arriving to the hospital within the Golden Hour. Most of the severely injured or heart disease patients may lose the life due to traffic jams. To avoid this problem need to make smart ambulance system for the patient carrying purpose. The Internet of Things (IoT) is recently developed technologies for monitoring and alerting process for various applications. The IoT technologies not only interconnect the Internet-enabled objects and optimizations from the collected data. This creates novel business models and even industries in the epoch of digital transformation. The similar goes with machine learning and how it allows the full consumption of the power of processors to detect things humans would not have been able to detect on their own.[2].

In day to day life the Real Time Health Monitoring and Tracking system is very important role in human life. This system will track, trace and monitor patients' health conditions. The various data will be collected by using special sensors and compared with a configurable threshold value. The collected data is forwarded to doctor then after verification of the data, doctor will guide the patient assistant for emergency help. The GSM is used to send the information for doctors and also show the location of the patient with help of GPS system. In this paper, the reviewed related technology in section III. The Smart ambulance system based on GSM, GPS and IoT Technology carried out in section IV. The conclusions, advantages and future scope in section V.

Literature Survey

The main objective of this paper is providing an efficient application for Real Time Monitoring and Tracking of Health issues. [3]. This system will track, monitor the patients and smooth the progress of taking care of their health; so efficient medical services provided at proper time. By using specific sensors, the various data will be captured and compared with a threshold value and observed value by microcontroller. If need any emergency, a short message service (SMS) will be sent to consent Doctor's through mobile number along with the observed values through with GSM module. In addition, the GPS provides the position information of the monitored person who is under surveillance all the time. The system will be bridge the gap between patients -in staged health change occasions- and health In [4], Face Detection System can be used to detect driver face, and compare with the stored face in memory. Normally car owner will be sleeping during the night time and somebody theft the car without any symptoms. The Face Detection Systems take photo images by one tiny web camera, which is hidden in car without known anyone. This System compared the obtained images with the stored images in memory. If not match the images, then information send to the authorized person through SMS techniques. The owners get the capture images tiny web camera of the thief in mobile phone and traced the place through GPS. The car location and speed of vehicles send to the authorized person then owner can be able to recognize the face of thief as well as the location of the car can find out with no trouble. [5] In this paper, Prashant Jadhav etl has proposed and implemented the traffic light control system by using image processing techniques.

The traffic density is deliberate based on captured images from the traffic camera and converted to the image sequences. The hardware section of this system consists of embedded processor, Infra Red sensor, camera and matlab software is used. Each image is individually processed and calculated the number of vehicles. When the vehicle density exceeds a specific density value and warning signal is produced automatically during the heavy traffic density. this system is less cost, simple setup construction and comparatively good accuracy along with speed.In[8], the proposed work is used to find best route identification based on multiple potential optimization factors such as journey time and distance. The active time organization scheme is operated in real times and emulates decision made by a traffic policeman. This system aims to save a working man-hours caused by traffic harms and accidents. It can be able to manage based on priority emergency vehicles. In the hardware section consists of various parts such as, embedded microcontroller, RFID tag, IR sensor, GSM and GPS is used. In [9], the smart

traffic system is proposed and implemented the traffic lights of mono directional roads. The system is calculating the traffic density by using IR sensors and posted on both side of the roads. Based on this information, the green light will be extended the time to permit large flow of cars during traffic jam, or reduced to stop needless waiting time when absents of cars at the opposite route of roads. The planned system is implemented, realized electronically and completed validation process successfully tested. As a final point, solar power panels is used for traffic light controller and powered by to decreases the grid electricity expenditure and recognizes green energy operations. In this paper [10], the have new proposed system able to clears the traffic overcrowding by rotating all the red lights to green lights on the path of the ambulance during the emergency. The system also includes of an android application. The details of ambulance are registered in network. During emergency condition, if the ambulance halts on the way, the android applications send an urgent situation command to the traffic signal server and also provide direction to destinations with help of Global Positioning System (GPS).

In [11] this paper, implemented the Energy Management System (EMS) for smart homes. This system, the device is interfaced with a data acquisition unit in every home. The data acquisition System on Chip (SoC) unit collects the energy utilization data from the each device and sends the data to a centralized server for additional processing the data and analysis. The proposed EMS utilizes off-the-shelf Business Intelligence (BI) and Big Data analytics software packages to enhanced energy consumption and collect consumer on demand. A prototype module was implemented and tested in the lab to mimic small housing area HVAC systems. The system empowers users to distantly monitor the control devices, and online bill generation with user friendly mobile application. In [12] this paper, proposed a smart ambulance model and provided automatic response actions to monitoring the patients from life threatening situations. There are various techniques such as Actuators, Biosensors, Intelligent unit, GPS and other components are used to achieve the model. Data Distribution Service (DDS) model were used for the connection between these heterogeneous elements of the systems. Furthermore, DDS normally, showed strong performance behavior and provides satisfy medical requirements of delivering monitoring data under convinced bounds.

PROPOSED METHODS

The proposed method consists of two important units such as health monitoring and also finding shortest path to reach hospital with help of IoT technologies in smart ambulance systems.

Health Monitoring

Health Monitoring is very important in day to day life to save the people during the critical situations. The health monitoring system is adopted in smart ambulance for monitoring the patient conditions and also send the message to doctors then guide the patient assistant while travel from incident place to hospitals. The message is forwarded to doctors through GSM technologies. In this system various sensor is included for various parameter observation purposes. The healthcare application of IoT is included in this paper of [13, 14].

To detect the heart rate (Monitor the heart rate changeability), The electrical activity of the heart rate is observed based on ECG and conveys necessary information about the status of heart rate and the function of its muscular contractions [15]. EMG is used to measure the electrical signal causes bymuscular activity [16] for gesture recognition, detection of neuromuscular diseases, etc. [15]. EEG is used to capture the electrical voltages which represent the brain activity and also monitoring Blood Pressure then Respiration Rate. The various sensors is integrated with microcontroller to monitor patient condition. The Health monitoring systems is show in the figure.

Fig. 2. GSM Modem is a specific type of modem, which accepts a SIM card operates based on a subscriber's mobile number under a network, similar a cellular phone. This GSM Modem is a RS232-logic level companionable, i.e., it will takes from -3v to -15v for high logic and from +3v to +15 for low level logic. MAX232 can be used to convert the

TTL into RS232 logic level converter between the microcontroller and GSM modem. The pin 11 of the microcontroller is sent signal to the GSM modem through pin 11 of max232. The signal is received at pin2 (RX) of the GSM modem. This modem can able to transmits the signal from pin3 (TX) to the microcontroller by using MAX232[6]. [7] GPS is a direction-finding system based on satellite and which is consists of twenty four satellites are located into the orbit. This system gives valuable information to the military operations, civil and business customers in and around the world and it can be freely accessible to any person by using GPS receiver. GPS can be able to work in any weather conditions at everyplace in the world. GPS receivers have to be locked the signals at least three satellites for estimate 2D position (latitude and longitude) and tracked movement. With 4 or more satellites in sight, the receiver can able to determine the user's 3D position (latitude, longitude and altitude). Once position of vehicle has been determined, the GPS unit determines other various information like, speed, time and other.

Google Map And IoT Techniques

The ambulance pickup the patient from the injured places and should drop in hospitals very quickly without any delay. Now a day's traffic jam is very important role day to life due to increasing the vehicles in road. It is very difficult to move hospital within specific time periods. To avoid this problem a new technique is proposed. In this system, the video camera and audio speaker must be installed permanently in the traffic jamming places. The ambulance driver can monitor the traffic jam in particular places through mobile app with help of IoT Techniques. Driver can take the decision to change the route to hospitals with help of Google map while the traffic is not clear. If the alternate route is not available, driver send voice message to the traffic jam places and also send to traffic police.

CONCLUSION

In this paper the ambulance system is proposed to save the patient life. In this system integrated various units such as embedded, GPS and IOT technology for finding a shortest route and distance to reach the hospital or injured places. Live tracking and status information of all route, distance and traffic status of the possible path are provided to the ambulance driver which helps in acquiring right path to reach the hospital or particular places without any delay. Google map is used to find the various route and distance of the hospitals. IOT systems are used to monitor the traffics of the places such as jamming places and bridges, etc. GPS and IOT system are interfaced with Microcontroller. According to the traffic information, driver can change the route to reach the hospital very quickly without any delay. The audio voice will be provided in to the jamming places (Permanent audio installed jamming places) before moving to hospital and also gives the information to traffic police to make necessary action along the way. This system is very useful to save the people life which can be adopted for real time application.

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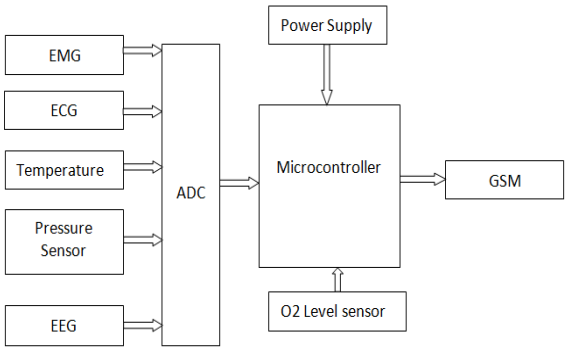

Fig.1. The Health monitoring system

Fig. 2. GSM Modem

Fig.3. GPS module

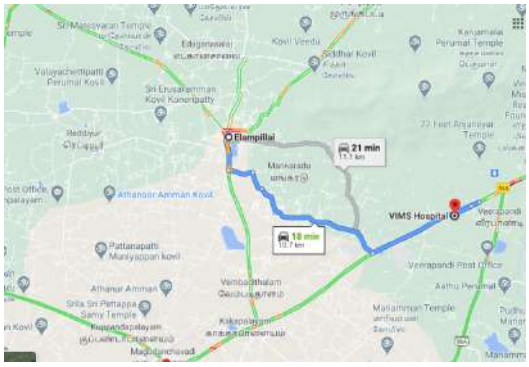

Fig. 4. Google Map And IoT Techniques

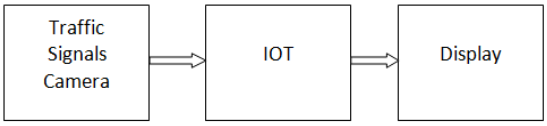

Fig. 5. Transmitter

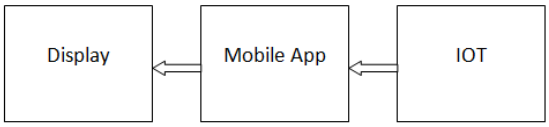

Fig. 6. Receiver Section

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RESEARCH ARTICLE

Fatty Acid Analysis of Ancient Indian Medicinal Plant in View of Aromatherapy

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ABSTRACT

Right from the vedic period, in India the traditional knowledge on medicinal plants has been passed on through generations. Ayurveda contains knowledge of the principles and methods of performing therapies though the medicinal plants and natural sources. In the current research the work focused on the medicinal plants which were used in the brain disorders. Plants were subjected to the extraction of lipids through the solvent extraction method and it was analyzed for the fatty acids by Gas Chromatography (GC). The percentage of the fatty acids in the extracts were in the range of MCFA (medium chain fatty acid):47.04-99%, LCFA (Long Chain Fatty acid):0.86-47.85%, PUFA (Polyunsaturated Fatty Acid):10.78-64.58%, MUFA (Monounsaturated Fatty acid): 1.37-67.01%,SFA(Saturated Fatty acid):5.27-76.93%.in conclusion the most of the medicinal plant *Bacopamonnieri* (Bhrami) showed PUFA concentration up to 64.58% which is very important in brain metabolism. In this study will help people following their traditional knowledge like Ayurveda, aromatherapy, Yajna Therapy, Thai massage, traditional practices etc. can have the molecular approach to their treatments.

Keywords: Ayurveda; Fatty acids; Gas chromatography; Yajna Therapy

INTRODUCTION

According to ayurveda (alternative medicine) and ancient system of Indian medicine each herb/plant on this earth can be used as medicine for psychological and physiological problems. Despite of this traditional medicine in India about 60-70millioin Indians suffer from severe and common mental disorder and receive treatment for their condition [1]. Psychiatric disorders account for 12% of the Global Burden and this is likely to increase to 15% by 2020.

It is also told that by 2025, mental illness (psychological problems) will catch up with heart disease or it may even overtake which is the biggest global health concern (World Health Report, 2001). *Dhupana* (Herbal Smoking) and *Yajna*(Sacrificial Fire) are seems to be designed by the ancient Indian Scholars or *Rishis* (Sages) to fight with the brain diseases. The psychotherapeutic agents (ayurvedic medicinal plants) used in these *Yajna* therapy/ aromatherapy/ herbal smoke treatment were aimed to the central nervous system(CNS) through nasal route i.e. directly delivering the drug to central nervous system to increase the bio-availability of a drug or active ingredient. It is rightly accepted during the transformation that the nature has best answers to all the diseases affecting human body from time to time. Over 50% of human brain's dry weight is comprised of lipids, and it is mainly enriched with long chain omega-3(n-3) polyunsaturated fatty acids(PUFA),suggesting a key role in the optimal, maturation and aging of neural structures and brain neural net [2].The fatty acids have been found to be effective reducing inflammation, building new blood vessels, improving transportation of nutrition into cells. Wide range of studies have attributed similar wound healing, anti-aging, anti-inflammatory and anti-skin cancer effects on plant-based oils like olive oil, sesame oil, coconut oil, sunflower seed oil, and more [3].

DHA is enriched in neural membrane structures found at synaptic gaps, mitochondria and endoplasmic reticulum(ER)4, and it can ultimately affect cellular quality and physiological characteristic including fluidity of membranes, lipid raft function, neurotransmitter release, transmembrane receptor function, gene expression, signal transduction, myelination, neuroinflammation and neuronal differentiation and growth [5,6]. Hence, it is very important to maintain proper lipid content and composition in these neuronal networks during development and maturation of the brain from gestation through childhood and adolescence7,8. DHA levels also plays a critical role in aging of the adult brain [9,10].The metabolization of DHA in human brain is said to be 0.004g/Day so the estimated half-life of brain DHA was found to be 2.5years [11], much more longer than that of DHA in peripheral tissues. Therefore, many researchers deduce that a quality DHA consumption is essential for reaching and conserving ideal brain DHA concentration and related neurological activities [12,13]. DHA in the body also likely has cardiovascular benefits throughout adulthood leading to better perfusion of the brain. These benefits include lower blood pressure, improved vaso reactivity, dampened hepatic triglyceride synthesis, and reduced platelet aggregation [14,15]. In the importance of fatty acids the current work we have made an effort to check the fatty acid content of the Indian medicinal plants.

MATERIAL AND METHODS

Essential oil sources

Listed plant materials were collected from local market. All the materials were dried at room 40^{0}C and powdered using grinder. Essential oils of Basil, sandal wood, Bhramhi, Bergamount, citronella was purchased from the local market. Also, the same plant powders of BH: *Bacopa monnieri* (Bhrami), SH: *Asparagus racemosus* (Shatawari), AS: *Withaniasomnifera* (Ashwaganda),YM: *Sinapis alba* (yellow mustard) BA: *Prunus dulcis* (Badam), AB: *Tinosporacordifolia* (amruthaballi) GD: *Cynodondactylon* (GarikeDruva), MD: *Gymnemasylvestre* (madhunashini), MX: mixed Hawansamagri , HK: *Terminalia chebual* (Haritaki) were collected from the local market ayurvedic stores. 25g of the samples were homogenized with petroleum ether (60-80^{0}C). The homogenized samples were transferred to separating funnel and it was allowed to settle. The supernatant /extract was collected and used for the determination of fatty acids. The residual powder was dried in oven and it was weighed also checked for the any presence of lipid by TLC (Thin Layer Chromatogrpahy).

Preparation of fatty acid methyl esters

The FAMEs were prepared as described by Christie [16] after one step liquid-liquid extraction sample. The supernatant/extract was taken for the sample preparation. The solvent fraction was removed in rotavapor (Buchii, R 210) at 35^0 C at 40 kPa pressure. The components collected in the round bottom flask were re suspended in 2 ml of 5% methanolic sulfuric acid and refluxed at 90° C for 30 min in water bath. Upon cooling the sample, desalting was

done with 1 ml of saturated NaCl solution. This mixture was extracted with equal volume of hexane (Merck, India) and the organic layer was collected and concentrated by purging N_2 gas. The solvent fraction was used for gas chromatographic estimation.GC-FID analysis was done using the hexane extract. Column configuration used was DB-23, length of 30 mm, 0.25 mm diameter and 0.25 μm of thickness(Agilent technologies Inc). Initial oven temperature during the analysis was 130 °C hold for 1 min with rate of heating as 6.5°C /min to 170 °C. Again heat to 215 at the rate of 2.75 hold for 4 min, heat to 230 °C at a rate of 40 °C hold for 3 min. Injector temperature used was 270 °C while detector temperature was 280 °C and a split of 1:25 and sample volume injected being 1 μl. Fatty acid standard mix with fatty acid methyl esters ranging from C4-C24 supplied by Sigma Chemical Company India was used for comparing the retention time of the sample peaks.

RESULTS AND DISCUSSION

All the plant materials were stored at 4°C. The homogenized samples were extracted for total lipid using Petroleum ether (60-80°C). The residue was checked for any traces of lipid by TLC. The methanol sulfuric acid and vanillin sulfuric acid detection agents did not show any traces of lipids in the spotted region. This shows that the residue left over after extraction with petroleum ether did not had any traces of lipid. the weight of the extract of each sample for every 25g was found to be in the range of 15-30%.*Bacopa monnieri* (Bhrami) -6.05g, *Asparagus racemosus* (Shatawari)-4.65g, *Withaniasomnifera* (Ashwaganda)- 3.75g, *Sinapis alba* (yellow mustard)-7.56g, *Prunus dulcis* (Badam)-7.05g, *Tinosporacordifolia* (amruthaballi)-5.43g, *Cynodondactylon* (Garike Druva)-4.63g, *Gymnemasylvestre* (madhunashini),-4.76g, mixed (*Hawansamagri*)- 4.61g, *Terminalia chebual* (Haritaki)-4.03g. Majority of the lipids produced in the world is by plants. These plants produced lipids are good source of calories and essential fatty acids for human beings and animals. Variety of fatty acids produced by plants with major common constituents like Palmitic, oleic, linoleic and linolenic acids. Classification of Fatty acids is based on the presence of double bonds between the carbon chain. When there are no double bonds, they are saturated fatty acids (SFA). The presence of one double bond is monounsaturated fatty acids (MUFA) and if two or more double bond then they are polyunsaturated fatty acids (PUFA). Regarding the size of the carbon chain, PUFAs have 16 and more number of carbons and are called long chain polyunsaturated fatty acids (LCPUFA).Those with more than 20 are referred to as very long chain polyunsaturated fatty acids (VLCPUFA). The PUFAs omega-3 and omega-6 are distinguished by their beneficial effects on human health, including their role in the synthesis of tissues and neuronal function.

From the figure.1 it is noted that the medium chain fatty acid was ranged from 40-90% in different extracts. *Badam* being a highest concentration of MCFA of 90% and the lowest being yellow mustard is 40%. medium chain fatty acids such as caprylic, carpric and lauric acid is manufacturing of soaps, detergents, surfactants, lubricants etc. and its primary source are coconut and palm kernel oils. Medium chain triglycerides have potentially important applications in medical, nutritional and dietetic fields, which include as a tool in the control of obesity as a factor in the lowering and inhibition or limitation of cholesterol deposition in the tissues for providing quick, high energy in both animals and humans and treatment of childhood epilepsy [17,18]. Liver is the place of oxidation of Medium chain fatty acids (MCFA). Animal and human studies have shown that the fast rate of oxidation of MCFA leads to greater energy expenditure. Also animal studies shows that greater energy expenditure results in less body weight gain and decreased size of fat depots after months of consumption [19]. Stearic acid a 18-carbon saturated fatty acid is present in all the plant extracts from 3%-10% concentration. In contrast to other long chain saturated fatty acids does not raise plasma LDL cholesterol. Dietary stearic acid leads to reduction of visceral adipose tissue have conclude that the stearic acid in diet dramatically reduce visceral fat likely by causing the caspase-mediated cell death of preadipocytes [20].

The fatty acid with more than 20 carbon are referred to as long /very long chain fatty acids. From the figure 2 it is clear that the BH,BA,SH, HK, SH,AS has very least amount of long chain fatty acids. Nervonic acid (NA) (C24:1n-9) is essential for the growth and maintence of brain physiology and peripheral nervous tissue. It bonds to sphingosine, forming sphingomyelin, which is a necessary component of myelin fatty acid in human beings during the normal

brain development [21]. Behenic acid (C22-1) is a saturated fatty acid. As a fatty acid it is important to help provide a protective barrier against the environment in order to maintain good skin quality. Behenic acid is present in natural oils and improve hydration, lubrication, emollient and soothing effect for the skin [3].

From the figure 3 it is noted that all the medicinal plant extract contains PUFA. Skin permeation of drugs can be improved by modifying intercellular lipid packing to reduce the barrier function in stratum corneum lipid domains [22,23]. Some scientific works [24,25,26] outlined a high epithelial penetration ability of polyunsaturated fatty acids (PUFAs) and an interesting enhancement effect in the skin drug permeation [25]. Over 50% of the brain's dry weight is composed of unsaturated fatty acids, lipids and it is especially enriched in long chain polyunsaturated fatty acids (PUFA). Key role for these molecules in the optimal development, maturation and aging of neural structures and networks is found significant. BH being very important in brain development it showed the presence of three polyunsaturated fatty acids in different concentration Linoleic acid (38.75%), alpha linolenic acid (24.29%) and arachidonic acid (1.54%).Fatty acids also help to carry medicine across the blood-marrow and blood-brain barriers to these extremely hard to reach tissues of the body. Fatty acids can be used to deliver nervous system and marrow supportive herbs like Brahmi, Gotu Kola, Ashwagandha, and more [27].Rest of the plant extracts showed the presence of linoleic acid (C18-2) in varied concentration from 10%-26%. Whereas AB did not show the presence of any PUFA. Flaxseed oil and canola, soy, perilla and walnut oils being a very good source of Alpha-linolenic acid which is a type of omega-3 fatty acid found in plants. It is similar to the omega-3 fatty acids that are in fish oil called eicosatetraenoic acid (EPA) and docosahexaenoic acid(DHA) [28]. The brain can synthesize DHA from alpha-linolenic acid which acts as metabolic precursors. The scientific proofs shows that due to the limited ability to produce DHA in human body the dietary DHA plays a role for development of the central nervous system. In gray and white matter of the brain DHA is incorporated at high levels. We can also found depositions in the rods and cones of the retina in the eye during growth, in particular during late pregnancy and the first two years of life indicating the essentiality for the normal brain development [29,30]. Highly concentrated (approximately 10%) DHA in the brain regulates many neurological processes including neuronal survival, synaptogenesis, neuronal plasticity and neuroinflammation also it is a dominant fatty acid of retinal phospholipids and affects rhodopsin content at discs, as well as photoresponses [31,32]. In rats dietary supplementation with EPA ethyl ester also down-regulates lipogenic genes, and decreases plasma cholesterol and triglyceride levels [33].Moreover demonstration of crossing the EPA and DHA crossing the blood-brain barrier(BBB) by simple diffusion, mediating neuroprotection through prolonging the lifespan of glia cells, and inhibiting microglia and inflammatory cells will say the importance of fatty acids [34].

The occurrence of MUFA is more compared to the PUFA in the plant extracts. From the figures 3 and 5 it is evident that the BH being more prominent in the PUFA concentration (50%) but when MUFA is considered the concentration is nearly 10%. But all other plant extracts the showed high concentration from 10 to 80% of MUFA whereas PUFA concentration was in the range of 10-25%. Vegetable oils being rich in MUFA not only are important in human nutrition but also can be used as renewable sources of industrial chemicals. Palmitoleic acid has the nutritional and industrial chemical advantages of the much more common longer chain MUFA, oleic acid (C18:1).Study findings have demonstrated that in cooler climates the production of omega -6 polyunsaturated fatty acids (PUFA), including linoleic acid, is higher while under warmer climate conditions, oleic acid from the group of monounsaturated fatty acids (MUFA) predominates [35].

CONCLUSION

The medicinal plants being a good source of fatty acids which are very much important in metabolism of nervous system. There is substantial evidence regarding fatty acids importance during growth on the development of the brain and resulting cognitive function. Nutrition and diet can also be affected by education and socioeconomic factors that can influence cognitive abilities, not to mention a propensity for a healthier lifestyle in general. DHA can alter the expression of genes encoding enzymes important for Hcy metabolism, methionine adenosyltransferasae (MAT) and methhyltetrahydrofolatereductase (MTHFR). Most of the traditionally used medicinal plants showed the

presence of fatty acids like PUFA can cross the BBB system by aroma oils, plant decoction, herbal smoke, herbal massage can be helpful in treating brain disorders. The data also gave idea to work on the entry of fatty acids through BBB system in humans also effect of these fatty acids in brain disorders/metabolism. The aroma oils extracted from medicinal plants when used for the aromatherapy has shown beneficial effect on stress management and prevent stress-related psychiatric problems via body-brain interaction and significant influence on multiple neurobiological indices, such as salivary cortisol and plasma BDNF as well as quantitative psychological assessments. This study will help people to think at the molecular level treatment in their traditional knowledge like Ayurveda, aromatherapy, Yajna Therapy etc.

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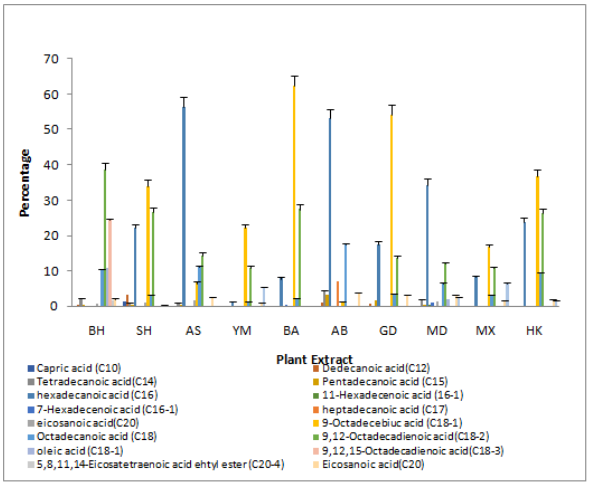

Figure 1. Showing medium chain fatty acids in the plant extracts BH: *Bacopamonnieri* (Bhrami), SH: *Asparagusracemosus* (Shatawari), AS: *Withania somnifera* (Ashwaganda), YM: *Sinapis alba* (yellow mustard) BA: *Prunusdulcis* (Badam), AB: *Tinospora cordifolia* (amruthaballi) GD: *Cynodondactylon* (GarikeDruva), MD: *Gymnemasylvestre* (madhunashini), MX: mixed Hawansamagri , HK: *Terminalia chebual* (Haritaki).

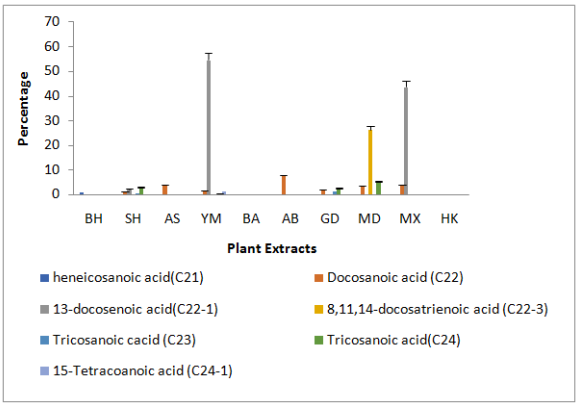

Figure 2. Showing long chain fatty acids in the plant extracts BH: *Bacopa monnieri* (Bhrami), SH: *Asparagus racemosus* (Shatawari), AS: *Withaniasomnifera* (Ashwaganda), YM: *Sinapis alba* (yellow mustard) BA: *Prunus dulcis* (Badam), AB: *Tinosporacordifolia* (amruthaballi) GD: *Cynodondactylon* (GarikeDruva), MD: *Gymnemasylvestre* (madhunashini), MX: mixed Hawansamagri , HK: *Terminalia chebual* (Haritaki).

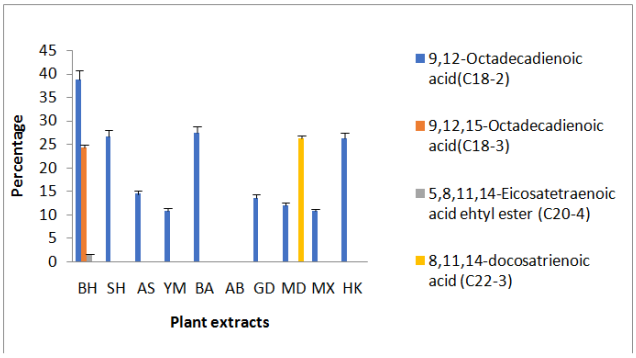

Figure 3. Showing polyunsaturated fatty acids (PUFA) in the plant extracts BH: *Bacopa monnieri* (Bhrami), SH: *Asparagus racemosus* (Shatawari), AS: *Withaniasomnifera* (Ashwaganda), YM: *Sinapis alba* (yellow mustard) BA: *Prunus dulcis* (Badam), AB: *Tinosporacordifolia* (amruthaballi) GD: *Cynodondactylon* (GarikeDruva), MD: *Gymnemasylvestre* (madhunashini), MX: mixed Hawansamagri , HK: *Terminalia chebual* (Haritaki).

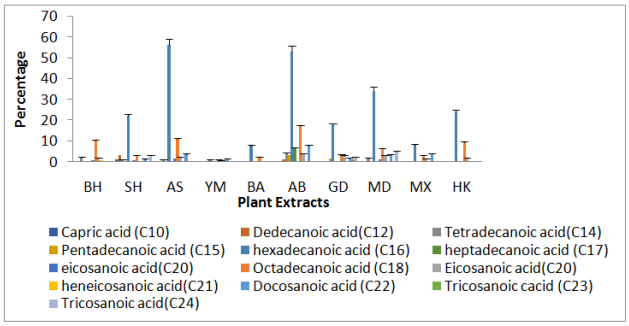

Figure 4. Showing saturated fatty acids (SFA) in the plant extracts BH: *Bacopa monnieri* (Bhrami), SH: *Asparagus racemosus* (Shatawari), AS: *Withaniasomnifera* (Ashwaganda), YM: *Sinapis alba* (yellow mustard) BA: *Prunus dulcis* (Badam), AB: *Tinosporacordifolia* (amruthaballi) GD: *Cynodondactylon* (Garike Druva), MD: *Gymnemasylvestre* (madhunashini), MX: mixed Hawansamagri , HK: *Terminalia chebual* (Haritaki).

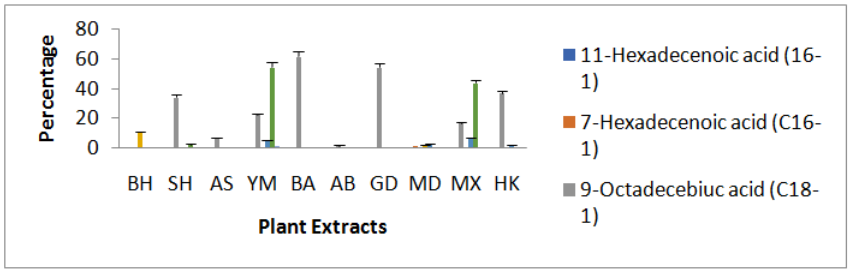

Figure 5. Showing Monounsaturated fatty acids (MUFA) in the plant extracts BH: *Bacopa monnieri* (Bhrami), SH: *Asparagus racemosus* (Shatawari), AS: *Withaniasomnifera* (Ashwaganda), YM: *Sinapis alba* (yellow mustard) BA: *Prunus dulcis* (Badam), AB: *Tinosporacordifolia* (amruthaballi) GD: *Cynodondactylon* (GarikeDruva), MD: *Gymnemasylvestre* (madhunashini), MX: mixed Hawansamagri , HK: *Terminalia chebual* (Haritaki).

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RESEARCH ARTICLE

Ultrasonic Study of Ternary Liquid Mixture Containing DMF, Butanol with Pyridine

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ABSTRACT

The ultrasonic velocity (U), density (ϱ) and viscosity (η) have been measured for the ternary mixture of N, N-dimethylformamide and butanol with Pyridine at different temperatures and at frequency 2 MHz for different concentrations of component liquids. The experimental data of velocity, density and viscosity have been used for a study of the molecular interaction in the different mixtures using thermoacoustic parameters such as adiabatic compressibility (β), free length (L_f), acoustic impedance(Z), free volume (V_f), surface tension(S) etc. Variation in the above parameters for the different mixtures is indicative of the nature of interaction between them.

Keywords: Ternary mixture, ultrasonic velocity, adiabatic compressibility, surface tension.

INTRODUCTION

Ultrasonic investigation of liquid mixtures consisting of polar and non-polar components, are of considerable importance in understanding the intermolecular interaction between the component molecules and find applications in several industrial and technological processes [1-7]. The variation in ultrasonic velocity and related parameters throw light upon the structural changes associated with the liquid mixtures having strongly as well as weakly interacting components. This has been studied for various ternary mixtures [8-9] with respect to variation in concentration and temperature. The ultrasonic techniques [10-17]are used frequently because of their ability of characterising the physico-chemical behaviour of the liquid system. The measurement of ultrasonic velocity in liquid mixtures reveals the degree of deviation from ideality whenever there are interactions among the component molecules. In the present paper various acoustic and the derived thermodynamic parameters are studied for ternary liquid mixtures containing Pyridine with DMF and Butanol. N, N-Dimethylformamide (C_3H_7NO)is a non-aqueous solvent which has no hydrogen bonding in pure state. Therefore, it acts as an aprotic, protophilic medium with high dielectric constant. Pyridine (C_5H_5N) is a polar aprotic solvent. It is used in wide variety of reaction including electrophilic substitution, nucleophilic substitution, oxidation and reduction as it has the property to form

complexes with many salts. It has a dipole moment 2.2 D at 298 K, which is small, compared to that of DMF. Since pyridine molecules are spherical in shape and monomers. They have weak interaction with their neighbours. n-Butanol is a primary alcohol with the chemical formula C_4H_9OH and a linear structure. butanol is used as a raw material for coating resins, butyl carboxylates such as butyl acetate, butyl acrylate, and glycol ethers. On the other hand, it is widely used as a solvent because many organic materials are soluble in it.Pyridine is a basic heterocyclic organic compound with a lower dielectric constant and dipole moment. Pyridine molecules are spherical in shape and tightly packed.

MATERIALS AND METHODS

The mixtures of various concentrations in mole fraction were prepared by taking analytical reagent grade and spectroscopic reagent grade chemicals with minimum assay of 99.9% and obtained from E-Merck Ltd (India). All the component liquids were purified by the standard methods [9]. In all the mixtures, the mole fraction of the second component, butanol ($X_2 = 0.4$), was kept fixed while the mole fractions of the remaining two (X_1 and X_3) were varied from 0.0 to 0.6, so as to have the mixture of different concentration. There is nothing significant in fixing the mole fraction of the second component at 0.4. The density, viscosity, and ultrasonic velocity were measured as a function of concentration of the ternary liquid mixture at different temperatures. Ultrasonic velocity measurements were made using an ultrasonic interferometer (Model M-84, supplied by M/S Mittal Enterprises, New Delhi) with the accuracy of $\pm$ 0.1 m·s^{-1}. The measuring cell of interferometer is a specially designed double-walled vessel with provision for temperature constancy. An electronically operated digital constant temperature bath (Model SSI-03 Spl, supplied by M/S Mittal Enterprises, New Delhi), operating in the temperature range of −10°C to 85°C with an accuracy of ±0.1°C has been used to circulate water through the outer jacket of the double-walled measuring cell containing the experimental liquid. The density and viscosity of liquid mixtures were measurement with Rolling-ball micro-viscometer.

Theory

The thermodynamic parameters were calculated by using following standard relations [18-27]

(i) Adiabatic Compressibility (β): $\beta = 1/U^2.\varrho$ ---------- (1)
(ii) Intermolecular free length (L_f): $L_f = K_T\beta^{1/2}$ ---------- (2)
(iii) Free Volume (V_f): $V_f = (M_{eff}.U/K.\eta)^{3/2}$ ---------- (3)
(iv) Internal Pressure (π_i): $\pi_i = bRT\,(k\eta/U)^{1/2}\,(\varrho^{2/3}/M^{7/6})$ ------ (4)
(v) Relaxation time (τ): $\tau = 4/3.\,(\beta.\eta)$ ---------- (5)
(vi) Acoustic impedance (Z): $Z = U.\varrho$ ---------- (6)
(vii) Gibb's free energy: $\Delta G = kT.Ln\,(kT\tau/h)$ ---------- (7)
(viii) Molar volume: $V_m = M_{eff}/\varrho$ ---------- (8)
(ix) Available Volume: $V_a = V_m(1-U/Um)$ ---------- (9)
(x) Rao's Constant: $R = V_m.U^{1/3}$ ---------- (10)
(xi) Wada's Constant: $W = V_m.\beta^{-1/7}$ ---------- (11)
(xii) Surface Tension: $S = 6.3 \times 10^{-4}.\varrho.U^{3/2}$ ---------- (12)

RESULT

The experimental values of density, viscosity and ultrasonic velocity are presented in table-1. The calculated values of thermoacoustic parameters are presented in tables-2 o 5. Temperature remaining constant, viscosity and velocity increase with increasing molar concentration of DMF. The above facts suggest a fairly strong interaction between solute and solvent molecules. However, concentration remaining constant, density and viscosity decreases, as temperature increases. This is because the interaction between solute and solvent molecules decreases due to thermal

energy of the molecules. The compressibility increases due to structural changes of the molecules leading to a decrease in ultrasonic velocity. Increasing value of Gibb's free energy with increases of temperature suggests closer approach of molecules indicating appreciable interaction between solute and solvent molecules. Temperature remaining constant, it increases slowly with increase in concentration of DMF. Internal pressure decreases as temperature increases which is obvious as the cohesion force decreases due to the increase in thermal energy, whereas internal pressure increases when concentration increase which indicates minimum cohesive force which is also observed while studying Gibb's free energy. Acoustic impedance (Z) is the product of ultrasonic velocity and the density of the given solution. It decreases with increase in temperature as well as increase in mole fraction of DMF. Decrease in acoustic impedance indicates weak interaction.

Free volume is the average volume in which the centre of a molecule can move due to the repulsion of the surrounding molecules. Effective free volume sometimes changes due to the transmission of collision effect through molecules. This is the reason why free volume increases sharply as temperature increases, whereas it increases slowly when concentration increases. Surface tension decreases as concentration of DMF increases, indicating decrease in molecular association which causes weak surface films. When temperature increases, attraction between molecules should decrease and hence surface tension should decrease.

CONCLUSION

It is obvious that, there exist a molecular interaction between the components of the mixture. In specific weak molecular interaction (like dipole-dipole, dipole-induced dipole and dispersive forces) are found to exist between components of the mixtures.

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Table-1: Experimental values of density, viscosity and ultrasonic velocity at different temperature.

Mole fraction		Density (Kg/m^3)				Viscosity(η) NSm^{-2} (x 10^{-3})				Velocity (ms^{-1})			
X_1	X_2	288K	298K	308K	318K	288K	298K	308K	318K	288K	298K	308K	318K
S-1: DMF + Butanol + Pyridine													
0.1000	0.3968	0.9021	0.8930	0.8838	0.8741	1.0693	0.9131	0.7939	0.6935	1370.4	1334.4	1324.9	1313.2
0.1960	0.3110	0.8975	0.8885	0.8794	0.8701	1.0834	0.9272	0.8024	0.7018	1336.1	1328.2	1321.6	1318.2
0.2882	0.2286	0.8935	0.8844	0.8753	0.8662	1.0631	0.9168	0.7933	0.6995	1328.3	1323.1	1320.5	1304.5
0.3768	0.1494	0.8929	0.8839	0.8748	0.8656	1.0425	0.9005	0.7829	0.6869	1319.8	1308.1	1294.8	1284.1
0.4620	0.0733	0.8883	0.8794	0.8703	0.8611	1.0453	0.8996	0.7824	0.6875	1310.8	1297.8	1281.4	1272.9
0.5440	0.0000	0.8846	0.8756	0.8666	0.8576	1.0329	0.8905	0.776	0.6858	1299.5	1282.1	1273.2	1261.5

Table-2: Calculated values of adiabatic impedance relaxation time and free length at different temperature.

Mole fraction		Adia. Compressibility x 10^{-10}				Relaxation time (x 10^{-12})				Free length(x 10^{-10})			
X_1	X_2	288K	298K	308K	318K	288K	298K	308K	318K	288K	298K	308K	318K
S-1: DMF + Butanol + Pyridine													
0.1000	0.3968	5.903	6.289	6.446	6.634	0.842	0.766	0.682	0.613	0.476	0.497	0.513	0.523
0.1960	0.3110	6.241	6.380	6.511	6.614	0.902	0.789	0.697	0.619	0.490	0.500	0.516	0.522
0.2882	0.2286	6.344	6.459	6.552	6.784	0.899	0.790	0.693	0.633	0.494	0.503	0.517	0.529
0.3768	0.1494	6.430	6.612	6.818	7.006	0.894	0.794	0.712	0.642	0.497	0.509	0.528	0.538
0.4620	0.0733	6.552	6.751	6.998	7.167	0.913	0.810	0.730	0.657	0.502	0.515	0.535	0.544
0.5440	0.0000	6.695	6.948	7.118	7.327	0.922	0.825	0.737	0.670	0.507	0.522	0.539	0.550

Table-3: Calculated values of acoustic impedance, Gibb's free energy and internal pressure at different temperature

Mole fraction		Acoustic Impedance (x 10^6)				Gibb's free energy (x 10^{-20})				Internal Pressure x 10^6			
X_1	X_2	288K	298K	308K	318K	288K	298K	308K	318K	288K	298K	308K	318K
S-1: DMF + Butanol + Pyridine													
0.1000	0.3968	1.236	1.192	1.171	1.148	1.163	1.201	1.238	1.275	1.882	1.812	1.740	1.674
0.1960	0.3110	1.199	1.180	1.162	1.147	1.166	1.202	1.239	1.275	1.912	1.824	1.746	1.676
0.2882	0.2286	1.187	1.170	1.156	1.130	1.166	1.202	1.238	1.276	1.894	1.811	1.731	1.677
0.3768	0.1494	1.178	1.156	1.133	1.112	1.165	1.202	1.240	1.277	1.881	1.805	1.736	1.674
0.4620	0.0733	1.164	1.141	1.115	1.096	1.166	1.203	1.241	1.278	1.883	1.805	1.739	1.676
0.5440	0.0000	1.149	1.123	1.103	1.082	1.167	1.204	1.241	1.279	1.875	1.801	1.732	1.677

Table-4: Calculated values of free volume, available volume and molar volume at different temperature.

Mole fraction		Free volume x 10^{-7}				Available volume				Molar Volume			
X_1	X_2	288K	298K	308K	318K	288K	298K	308K	318K	288K	298K	308K	318K
S-1: D MF + Butanol + Pyridine													
0.1000	0.3968	4.032	9.748	12.521	15.901	29.00	33.89	35.47	37.39	202.1	204.2	206.3	208.6
0.1960	0.3110	3.806	9.460	12.276	15.709	33.50	34.86	36.08	36.90	203.1	205.2	207.3	209.5
0.2882	0.2286	3.882	9.566	12.473	15.541	34.65	35.68	36.38	38.87	204.1	206.1	208.3	210.5
0.3768	0.1494	3.959	9.661	12.352	15.598	35.76	37.63	39.75	41.59	204.2	206.3	208.4	210.6
0.4620	0.0733	3.903	9.561	12.173	15.374	37.10	39.16	41.72	43.28	205.2	207.3	209.5	211.7
0.5440	0.0000	3.922	9.532	12.206	15.224	38.71	41.37	42.97	44.98	206.1	208.2	210.4	212.6

Table-5: Calculated values of Rao's Constant, Wada Constant and Surface tension at different temperature

Mole fraction		Rao's Constant				Wada Constant				Surface tension			
X_1	X_2	288K	298K	308K	318K	288K	298K	308K	318K	288K	298K	308K	318K
S-1: D MF + Butanol + Pyridine													
0.1000	0.3968	224.5	224.8	226.6	228.4	156.8	157.0	158.1	159.2	28.83	27.42	26.85	26.21
0.1960	0.3110	223.7	225.6	227.5	229.7	156.4	157.5	158.6	160.0	27.62	27.10	26.62	26.24
0.2882	0.2286	224.3	226.3	228.5	230.0	156.7	157.9	159.2	160.1	27.25	26.82	26.46	25.71
0.3768	0.1494	224.0	225.6	227.2	228.9	156.5	157.5	158.4	159.5	26.97	26.35	25.68	25.09
0.4620	0.0733	224.6	226.1	227.5	229.5	156.9	157.8	158.7	159.8	26.56	25.90	25.15	24.64
0.5440	0.0000	224.9	226.2	228.0	229.7	157.1	157.9	158.9	160.0	26.11	25.32s	24.80	24.21

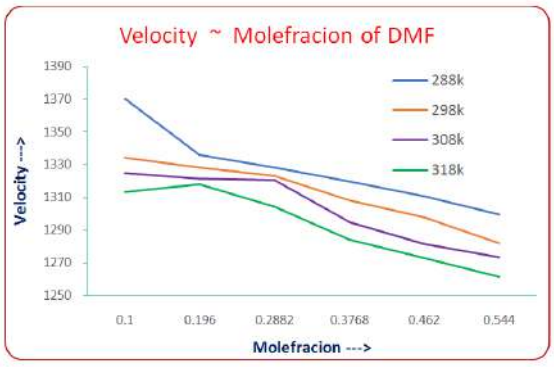

Fig. 1 . Velocity Molefraction of D MF

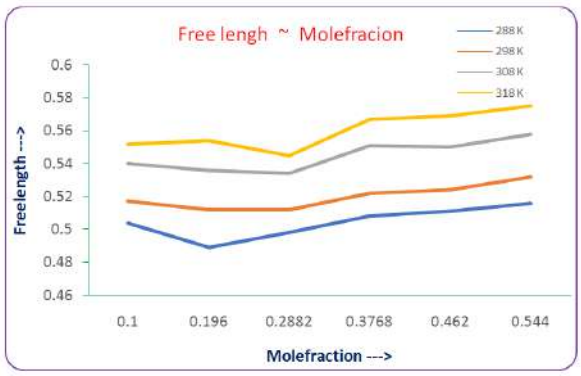

Fig.2 Free length Molefraction

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RESEARCH ARTICLE

Buzzard Optimization Algorithm Tuned 2DOF-FOPIDN Controller for a Multi Source Restructured Power System

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ABSTRACT

This article proposes the plan of the Buzzard Optimization Algorithm (BUZOA) procedure tuned Two Degree of Freedom Fractional Order PID with Filter (2-DOF-FOPIDN) regulators dependent on the Automatic Generation Control (AGC) of a multi-source thermal-hydro-wind interconnected restructured power framework. The fundamental obligation of AGC is utilized to keep up with the system frequency related with tie-line power deviations. The essential objective of the AGC framework is to limit the transient deviations in the area frequencies and tie-line power oscillations and to guarantee their steady-state errors to be zeros. A 2-DOF-FOPIDN regulator is a created PID abutting to its derivative, and integer orders are fractional numbers in position of whole numbers. The huge benefit of the 2-DOF-FOPIDN regulator offers adaptability in controlling purposes, which empowers plan the AGC framework and excellent competence in managing boundary vulnerability, eliminating steady state error, and guaranteeing improved stability. These proposed regulators are planned utilizing BUZOA procedure and carried out on the AGC framework. The reproduction results uncover that the predominance of 2-DOF-FOPIDN regulator, the unique presentation of AGC system of a two-region interconnected restructured power framework have worked on as far as less pinnacle deviation and settling time of region frequencies and tie-line power in various exchanges as contrasted and Proportional Integral (PI) regulator, Proportional Integral Derivative with Derivative Filter (PIDN) regulator.

Keywords: AGC, Automatic Generation Control, Buzzard Optimization Algorithm, 2-DOF-FOPIDN controller, PI controller, PIDN controller

INTRODUCTION

In the current situation, the power system course of action comprises the mass of generating utilities interconnected together through tie-lines. The advanced power system usually comprises of various interconnected subsystems with tie-lines. For each part of the subsystem is necessitates to incorporating the matching system generation with system load used to control the system frequency is known as the Automatic Generation Control (AGC) [1]. Restoration of system frequency utilized with apparent worth requirements beneficial control activity, which manages the load reference position point throughout the speed changer mechanism [2]. The AGC action is synchronized by the Area Control Error (ACE) with the aid of system frequency and tie-line flows. In every zone, AGC monitors the system frequency and tie-line flow and works out the net change in the generation required based on the change in demand along with the changes in the set position of the generators within the area used to keep the time average of the ACE at a low value. In this manner, ACE is described as a linear combination of power net-exchange and frequency deviations considered as the controlled output of AGC. As the ACE is headed to zero by the AGC, frequency and tie-line power errors will be compelled to zeros [3].

The regular AGC two-area interconnected power system is altered to consider the activity of AGC in an open market power system. Open transmission with other socialized companies for generation, transmission, and distribution affects the design of the AGC problem to house the new constraints along with the territorial functionality of each company. So the usual AGC two-zone interconnected power system is manipulated in accordance with the effect of bilateral contracts on the dynamics [4]. Each control territory has its very own AGC and is in charge of following its own load and respecting tie-line power trade contracts with its neighbors. Starting at now, these trades are done under the supervision of the Independent System Operator (ISO), Independent Contract Administrator (ICA) or other careful affiliations. There can be distinctive combines the understandings between each Disco and available Gencos, on the other hand, each Genco can contract with various Discos. With the development of the Disco Participation Matrix (DPM) the visualization of contracts can be made easier. DPM is represented as an asymmetrical matrix constructed by the number of rows equal to the number of Gencos and the number of columns equal to the number of Discos in the system. Each element in the matrix is referred to a fraction of a total load contracted by a Disco (Column) toward a Genco (Row). The sum of all the entries in a column of this matrix is unity. DPM proves the participation of a Disco in a contract with Genco.

The nominal operating point of a power system transforms from its pre-determined value subjected to any disturbance due to the deviation made by the operating point in the ostensible system frequency and scheduled power trade to different areas which is unfortunate. Thus, an AGC scheme primarily integrates a suitable control system for an interconnected power system having the ability to bring the frequencies of every area and the tie-line power back to unique set point values or very closer to set point values successfully after the load change. Robust secondary controllers are important to retain a flat frequency profile. Several advanced controller structures and techniques have been proposed in the literature for AGC system [5]. Among the choice of secondary controllers, the most commonly employed is the conventional Proportional plus Integral (PI) controllers. These PI controllers are still popular in the power industry for frequency regulation even in any change in system operating conditions, new gain values can be computed easily even for multi-area power systems. The PI controller is very simple for execution and gives a better dynamic response, but their performances deteriorate when the complexity in the system increases due to the natural impact of the disturbances. The fundamental downside of this PI controller is doesn't capable to predict the future errors of the system, can't eliminate steady-state oscillations and reduces settling time. Consequently, the overall stability system is relatively low [6].

The fundamental points of the PID regulator, a derivative mode, perk up the constancy of the system In any case, as the input signal have quick corner, the derivative expression resolve convey nonsensical dimension manage inputs to the system. Moreover, any clamor within the input signal will achieve tremendous system input signals that guide to disarray in realistic applications. The reasonable answer for this issue is driving the first order filter on the

derivative expression and tunes its pole so the chatting because of the noise doesn't happen in view of the fact that it attenuates high frequency clamor [7]. A PID with a derivative Filter (PIDN) regulator had been considered in that assessment. The exhibition of PIDN regulators can be perk up by means of partial investigation. Further could enhance the system performance, a fractional order PID regulators have been considered and it gives adaptability in controlling purposes which assists with arranging the AGC issues and excellent competence of managing parameter ambiguity, removal of steady state error, and ensures enhanced constancy [8]. Be that as it may, this adaptability empowers the tuning of the regulator even in complex circumstances [9]. Subsequently, the assignment of planning the FOPID regulator is really difficult, and the regulator structure doesn't particularly impose the fractional property. Nonetheless, in the closed-loop reference model, the regulator is fractional and has an exciting structure for its execution. For sure, the regulator can regularly be disintegrated into two sections. An integer order controller cascaded with a fractional order controller and ensured that the controller design method is simple to implement.

Lately, two degree of freedom (2-DOF) stand regulator structures have gained much consideration in the control society. The adaptability of 2-DOF greater than a (1-DOF) is according to the perspective of accomplishing elevated presentation in set point pathway and the guideline in the occurrence of interruption inputs [10, 11]. The prevalence and benefit of fractional order controller, alongside two-degree-of-freedom, are yet to be investigated in the field of AGC. In this examination, a 2-DOF-FOPIDN controller are planned and carried out in the optional regulator of AGC loop of the test system. Huge benefit of 2-DOF-FOPIDN controllers is exceptionally appropriate for controlling purposes which assists with planning the AGC issues and incredible ability of taking care of parameter vulnerability, eliminating steady-state errors, and ensures better stability. In this study a few regulators, for instance, proposed PI, PIDN and 2-DOF-FOPIDN controllers, are made to give a much powerful dynamic response. The proposed controller gains and other parameters were tuned with novel and effective meta-heuristic Buzzard Optimization Algorithm (BUZOA) [12] and its exhibition is contrasted and the PI and PIDN controller.

Modelling of Two-Area Restructured Power System

The schematic diagram of a two-region interconnected power system in the restructured environment has showed up in Fig 1. The restructured power system structure changed with the target that it would allow the creation of legitimately explicit undertakings for generation (Genco), transmission (Transco) and distribution (Disco).A Disco in every area can contract with Gencos in its own or various regions. The comparing DPM is given as follow

$$DPM = \begin{bmatrix} cpf_{11} & cpf_{12} & cpf_{13} & cpf_{14} \\ cpf_{21} & cpf_{22} & cpf_{23} & cpf_{24} \\ cpf_{31} & cpf_{32} & cpf_{33} & cpf_{34} \\ cpf_{41} & cpf_{42} & cpf_{43} & cpf_{44} \end{bmatrix} \quad (1)$$

Where cpf speaks to contract participation factor &bears a resemblance to signals might convey data regarding which the Genco needs to pursue the load demanded the Disco. The scheduled consistent state power flow on the tie-line is

$$\Delta P_{Tie\ 12}^{scheduled} = \sum_{i=1}^{2}\sum_{j=3}^{4} cpf_{ij}\,\Delta P_{Lj} - \sum_{i=3}^{4}\sum_{j=1}^{2} cpf_{ij}\,\Delta P_{Lj} \quad (2)$$

The tie-line (actual) power is given as

$$\Delta P_{Tie\ 12}^{actual} = \frac{2\pi T_{12}}{s}(\Delta F_1 - \Delta F_2) \quad (3)$$

At some intervention, the representation of tie-line error and error signal be as

$$\Delta P_{Tie\ 12}^{Error} = \Delta P_{Tie\ 12}^{actual} - \Delta P_{Tie\ 12}^{scheduled} \quad (4)$$

$$ACE_1 = \beta_1 \Delta F_1 + \Delta P_{Tie\ 1,2\ error} \quad (5)$$

$$ACE_2 = \beta_2 \Delta F_1 + \Delta P_{Tie\ 2,1\ error} \quad (6)$$

The GENCO generation for ithGenco to DPM passages be as

$$\Delta P_{Gi} = \sum_{j=1}^{4} cpf_{ij}\,\Delta P_{Lj} \quad (7)$$

Design of proposed controllers using Buzzard Optimization Algorithm

Control structure of PI controller: A Proportional and integral alludes to retune activity which includes the combination of error signal over some time. The rate of change of acceptable signals is proportional to the error signals. The blend of proportional and integral terms is essential to expand the response's speed and dispense with the steady-state error. The control structure of the PI regulator has appeared in Fig 2. The transfer function of PI regulator can be expressed as

$$G_{PI}(s) = K_P + \frac{K_I}{s} \quad (8)$$

The error inputs to the controllers are the individual ACE signals given by Eqn. (5) and (6). The control contributions of the power framework u1 and u2 with the PI structure are given in Eqn (3.9) and (3.10).

$$u_1 = K_{P1}\, ACE_1 + K_{I1} \int ACE_1\, dt \quad (9)$$

$$u_2 = K_{P2}\, ACE_2 + K_{I2} \int ACE_2\, dt \quad (10)$$

The BUZOA technique is utilized to decide the optimal parameters of PI regulator to limit the integral square of ACE signal. The presentation of these responses is measured using objective functions such as

$$J_i = \int_0^{t_{sim}} [(ACE_i)^2]\, dt \quad (11)$$

The PI regulator parameter bound, as a result the intend problem can be formulated as,

$$Minimize\, J_i \quad (12)$$

Subject to

$$K_{Pi}^{min} \le K_{Pi} \le K_{Pi}^{max}, K_{Ii}^{min} \le K_{Ii} \le K_{Ii}^{max} \quad (13)$$

Control structure of PIDN controller: The control construction of the PIDN regulator appears in Fig 3. Where K_P, K_I and K_D are the corresponding controller gain values and N is the derivative filter coefficient. The ACE signal of every region is used to the input signal of the PIDN regulator and output signal u_1 and u_2 could enhance the AGC loop of power framework. The transfer function of the proposed PIDN regulator is expressed as

$$T(s) = K_P + \frac{K_I}{s} + K_D\left(\frac{Ns}{s+N}\right) \quad (14)$$

The BUZOA technique is utilized to decide the optimal parameters of PIDN regulators' to limit the ACE signals of the proposed power system in Eqn (11). The problems limitations are the PIDN regulator parameter are bounds. Therefore, the propose problem can be formulate as the subsequent optimization crisis.

$$Minimize\, J_i \quad (15)$$

Subject to

$$K_P^{min} \le K_P \le K_P^{max}, K_I^{min} \le K_I \le K_I^{max}, K_D^{min} \le K_D \le K_D^{max}, N^{min} \le N \le N^{max} \quad (16)$$

Control structure of 2DOF-FOPIDN: The structure of a 2DOF-FOPIDN controller is shown in Fig.4. It comprises of set-point weights (p_w and d_w), controllers gains (K_p, K_i, and K_d), derivative filter coefficient (N_2) and fractional integral and derivative orders (λ and μ). In this Fig 4, C(s) is a single degree-of-freedom controller, D(s) is the load disturbance and F(s) acts as a pre filter on the reference signal. For a parallel 2DOF-FOPID, C(s) and F(s) are given by:

$$C_s(s) = K_p + \frac{K_i}{s^\lambda} + K_d s^\mu \left(\frac{N_2}{N_2 + s^\mu}\right) \quad (17)$$

$$F_s(s) = p_W K_p + \frac{K_i}{s^\lambda} + d_W K_d s^\mu \left(\frac{N_2}{N_2 + s^\mu}\right) \quad (18)$$

The BUZOA optimization technique is used to decide the optimal parameters of 2DOF-FOPIDN controllers with the goal to limit Integral Square of ACE signals are expressed in Eqn (11). The problem constraints are the 2DOF-

FOPIDN controller parameter bounds. Therefore, the design problem can be formulated as the following optimization problem.

$Minimize J_i$ (19)

Subject to

$$K_p^{min} \le K_p \le K_p^{max},\ K_i^{min} \le K_i \le K_i^{max},\ K_d^{min} \le K_d \le K_d^{max},\ N_2^{min} \le N_2 \le N_2^{max},\quad \lambda^{min} \le \lambda \le \lambda^{max},\ \mu^{min} \le \mu \le \mu^{max},\ p_W^{min} \le p_W \le p_W^{max},\ d_W^{min} \le d_W \le d_W^{max} \quad (20)$$

Buzzard Optimization Algorithm based design of 2DOF-PIDN controller: Buzzard Optimization Algorithm (BUZOA) algorithm is modeled by paraphrasing and simulated with the behavior of collective flight (group) buzzards (vultures) [12]. Let us assume *d* -dimensional buzzard search space. *i*th particle is described by the vector of position L_i as follows in this *d* -dimensional space:

$L_i = (l_{i1}, l_{i2}, l_{i3}, \dots \dots l_{id})$ (21)

C -vector is the ability of smell, and the ability of taste for the *i* -th particle is defined by the vector *C*as follows:

$C_i = (c_{i1,}, c_{i2,}, c_{i3,}, \dots \dots c_{id})$ (22)

The best position which *i* -th particle is found is the vector $C_{i,best}^*$ and are shown as follows:

$C_{i,best}^* = (c_{i1}^*, c_{i2}^*, c_{i3}^*, \dots \dots c_{id}^*,)$ (23)

The best position that has found the best particle inthe whole particle is $C_{g,best}^*$ and defines as follows:

$C_{g,best}^* = (c_{g1}^*, c_{g2}^*, c_{g3}^*, \dots \dots c_{gd}^*,)$ (24)

Whole particle best position: $C_{g,best}^*$, Each particle best position: $C_{i,best}^*$ and best position when compared to all particles: $C_{g,best}^*$,

Selection of position for best achieved at iteration no.1 (*t*=1) [12].

$C_{i,best}^* = L_i(t), \quad i = 1, 2, 3, \dots d$ (25)

$cost\,(C_{i,best}^*) = cost\,(L_j(t))$ (26)

The location change and each particle cost for iteration algorithm as

$$\begin{cases} if cost\left((L_i(t)\right) < cost\,(C_{i,best}^*) \Rightarrow \\ \quad else Not change \\ cost\,(C_{i,best}^*) = cost\left(L_j(t)\right) i = 1, 2, 3 \dots d \\ \quad C_{i,best}^* = L_i(t) \end{cases} \quad (27)$$

Each particle location update be as of,

$L_1(t) = \alpha_1 L(t-1) + \alpha_2 * rand * (C_{g,best}^* - C_i(t-1))$ (28)

$L_2(t) = L_1(t) + \beta * rand_1 * \left(C_s(t) - C_i(t-1)\right) + (1-\beta) * rand_2 * \left(C_v(t) - C_i(t-1)\right) + \gamma * rand_1 * \left(C_{g,best}^* - C_i(t-1)\right) + (1-\gamma) * rand_2 * \left(C_{g,best}^* - C_i(t-1)\right) L_i(t) = L_i(t-1) + C_i(t)$ (29)

α_1 : inertia weighting factor; α_2, β andγ: the training constant coefficient. $rand_1$, $rand_2$:2-random numbers bears uniform distribution in interval 0- 1. The function may change as equation [12].

$C_1(t) = \alpha_1 C(t-1) + \alpha_2 * rand * (C_{i,best}^* - l_i(t-1))$ (30)

$C_2(t) = C_1(t) + \beta * rand * \left(C_s(t) - C_i(t-1)\right) + (1-\beta) * rand * \left(C_v(t) - C_i(t-1)\right) + \gamma * rand * \left(C_{g,best}^* - l_i(t-1)\right)$ (31)

$C_i(t) = C_i(t-1) + L_i(t)$ (32)

$C_i(t-1)$, is the ability vectors in repetition $(t-1)^{th}$ and $L_i(t-1)$ is the Position vector in repetition$(t-1)^{th}$. To prevent the excessive increase in the ability and speed of a particle in the movement from one location to another location, the variation of the ability to the range is limited $C_{min} \leq C \leq C_{max}$. $C_s$is smell capability, is the vision capability and smell = 1-taste.

Modeling of a 2-Dof-Fopidn Controller based AGC Loop of a Two-Area Restructured Power System

The detailed transfer function representation of 2DOF-FOPIDN controller based AGC for two-area thermal-hydro-wind restructured is indicated Fig.5. The Gencos in area-1 clustered with a thermal and hydro power unit and area-2 with a thermal and wind power unit. In this investigation, a 2DOF-FOPIDN controller has been used as a secondary controller of the AGC system of each and every area. The regulating limits of 2DOF-FOPIDN controller are tuned to attain the goal - limit the ACE signal for the test system using the BUZOA technique.

SIMULATED OUTCOMES AND DISCUSSIONS

In this evaluation, AGC execution of a two-region multi-source thermal-hydro-wind restructured power system making use of PI/ PIDN/ 2DOF-FOPIDN controller for an alternate sort of exchange is thought of. The representations of the power system being scrutinized have been created in the MatLab/Simulink model. The parameter values of the two-region multi-source AGC framework are specified in the appendix. The most favourable solution of control inputs is engaged as an improvement issue, and the intention works in Eqn. (11) is gathered using the frequency variations of control regions and tie-line power variations. Considering the exchanges made between them, it will in general be requested into two sorts of exchanges. On the off chance that a Disco have a concurrence with the Genco of a comparable domain is called Poolco based exchanges, and if a Disco has a concurrence with a Genco of any more region is called bilateral-based transactions. A few optional regulators like PI, PIDN and 2DOF-FOPIDN are viewed as each in turn. The BUZOA technique is utilized to choose the ideal PI, PIDN and 2DOF-FOPIDN controllers' optimal parameters to restrict the ACE signal for the two-region multi-source thermal-hydro-wind restructured power system.

Scenario 1: Poolco based transactions

For this situation of Poolco exchange, Gencos of every area associate with Disco of that area. Consequently, the Disco of region 1 is demanding load, though the Disco of region 2 isn't requesting any load. In the test system, a load demand change of 0.25, p.u.MW in each Disco in region 1 has been thought of. The DPM considered for the Poolco exchange is given by Eqn. (33). $Disco_1$ and $Disco_2$ demand identically from their neighbourhood Gencos, viz., $Genco_1$ and $Genco_2$. Henceforth, it is considered here that all the area participation factor (apf) is equivalent to 0.5.

$$DPM_1 = \begin{bmatrix} 0.5 & 0.5 & 0.0 & 0.0 \\ 0.5 & 0.5 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 \\ 0.0 & 0.0 & 0.0 & 0.0 \end{bmatrix} \quad (33)$$

The optimized PI, PIDN and 2DOF-FOPIDN regulators are viewed as each in turn and carrying out in a planned test system and compared with that of the PI and PIDN controller. The comparative dynamic output responses of the area frequencies and tie line power variations of the test systems with a variety of sorts of controllers are shown in Fig.6. From the Fig 6, it can be observed that the projected 2DOF-FOPIDN controller has superior dynamic responses of frequency variations of each area and tie-line power variations when compared with that of PI and PIDN controller. The above examination exposed to facilitate 2DOF-FOPIDN controller have fewer peak deviation, the magnitude of oscillations, and more rapidly settling time than PI and PIDN controller and illustrate greater performance for overprotective system oscillations. Thus, 2DOF-FOPIDN can be making use of an appropriate inferior controller in both AGC loops.

Scenario 2: Bilateral based transactions

In these trades, all of the Discos have a concurrence with the Gencos and the accompanying with DPM implying Eqn. (5.30) is considered as

$$DPM_2 = \begin{bmatrix} 0.4 & 0.5 & 0.2 & 0.2 \\ 0.3 & 0.3 & 0.1 & 0.1 \\ 0.2 & 0.1 & 0.5 & 0.4 \\ 0.1 & 0.1 & 0.2 & 0.3 \end{bmatrix} \quad (34)$$

For the present circumstance, each Disco requests 0.25, p.u.MW for each from Gencos as portrayed by cpf in the DPM matrix and each Gencos takes part in AGC as characterized by the accompanying area participation factor $apf_{11} = apf_{12} = 0.5$ and $apf_{21} = apf_{22} = 0.5$. The BUZOA technique tuned PI, PIDN and 2DOF-FOPIDN controllers are executed in a proposed test system. The comparative transient performances of test systems with various sorts of controllers have shown up in Fig. 7. From the Fig 7, it is visible that the proposed 2DOF-FOPIDN controller is better than the PI and PIDN controller because of smaller peak variations, settling time, and decreased oscillations. From the Fig 7, it is visible that the proposed 2DOF-FOPIDN controller is better than the PI and PIDN controller. It might be seen that the frequency deviations of both area and tie line power digressions have been enhanced in terms of the less peak deviations, settling time, and magnitude of oscillations for the two area multi source thermal-hydro-wind restructured power system.

CONCLUSION

The 2DOF-FOPIDN regulators are planned and executed in a two-region multi-source thermal-hydro-wind restructured power framework The BUZOA technique has been utilized to decide the optimal parameters of the 2DOF-FOPIDN regulator. Examination uncovers on correlation of dynamic responses the proposed 2DOF-FOPIDN regulator in all exchange arrangements investigates the prevalence as far as less pinnacle deviations, settling time, and magnitude of oscillations of the test framework's contrasted with the PI and PIDN regulators. The huge benefit of 2DOF-FOPIDN regulators is adaptability in controlling reason, which assists with giving remedial measures to be taken up for the AGC issues and amazing ability of taking care of parameter vulnerability, elimination of steady-state error, and guarantees better stability.

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APPENDIX

Control area and Gencos parameters [9, 11]

Constraints	**Area1**	**Area 2**
Area-1 & Area-2 capacities	1000 MW	1000 MW
Generating machine rating for single area	500 MW	500 MW
Kp (Hz/p.u.MW)	120	120
Tp (sec)	20	20
β (p.u.MW / Hz)	0.425	0.425
R (Hz / p.u.MW)	$R_1=R_2=2.4$	$R_3=R_4=2.4$
Tg (sec)	$T_{g1}= 0.08$	$T_{g3} = 0.08$
Tt (sec)	$T_{t1}= 0.36$	$T_{t3} = 0.36$
T_r(sec)	$T_{r1}= = 10$	$T_{r3}= 10$
K_r	$K_{r1}= 0.5$	$K_{r3}= 0.5$
Synchronising coefficient (p.u.MW / Hz)	$2\pi T_{12}=0.545$	
System frequency (F) in Hz	60 Hz	
Area participation factor (apf)	$apf_{11}=apf_{12}=apf_{21}=apf_{22}= 0.5$	
Area capacity ratios	$a_{12} = -1$	
Hydro power generating unit	T_{Hg} =0.2 sec, T_1=0.513 sec, T_2=10 sec, T_w=1 sec,	
Wind power generating unit	T_{w1}=6.0 sec, T_{w2}=0.041 sec K_{w1}= 1.25, K_{w2}=1.4	

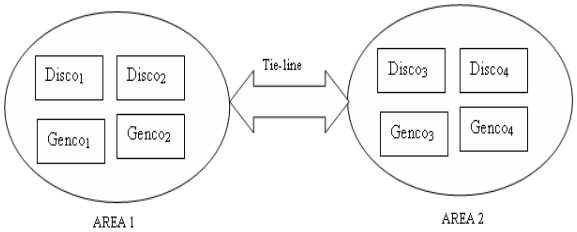

Fig 1: Schematic representation of two-area restructured power system

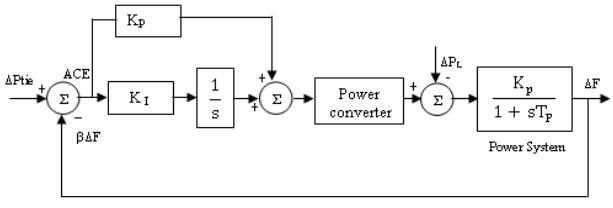

Fig 2: Block diagram for PI controller with AGC loop

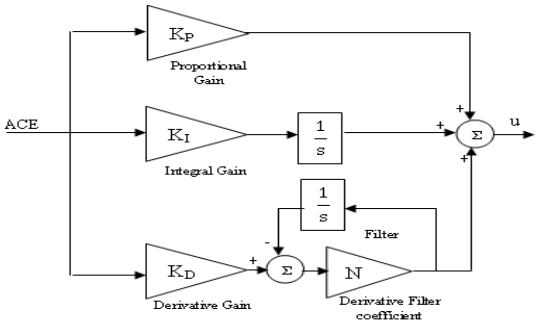

Fig 3: Block diagram for PIDN controller

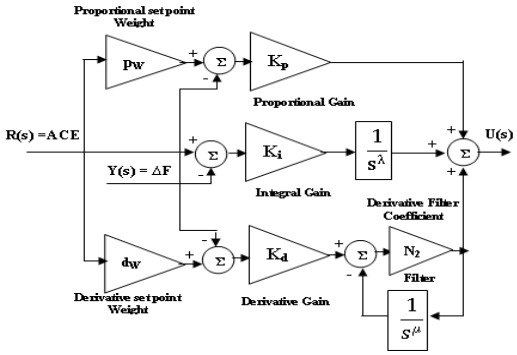

Fig 4: Scheme representation of 2 DOF-FOPIDN controllers

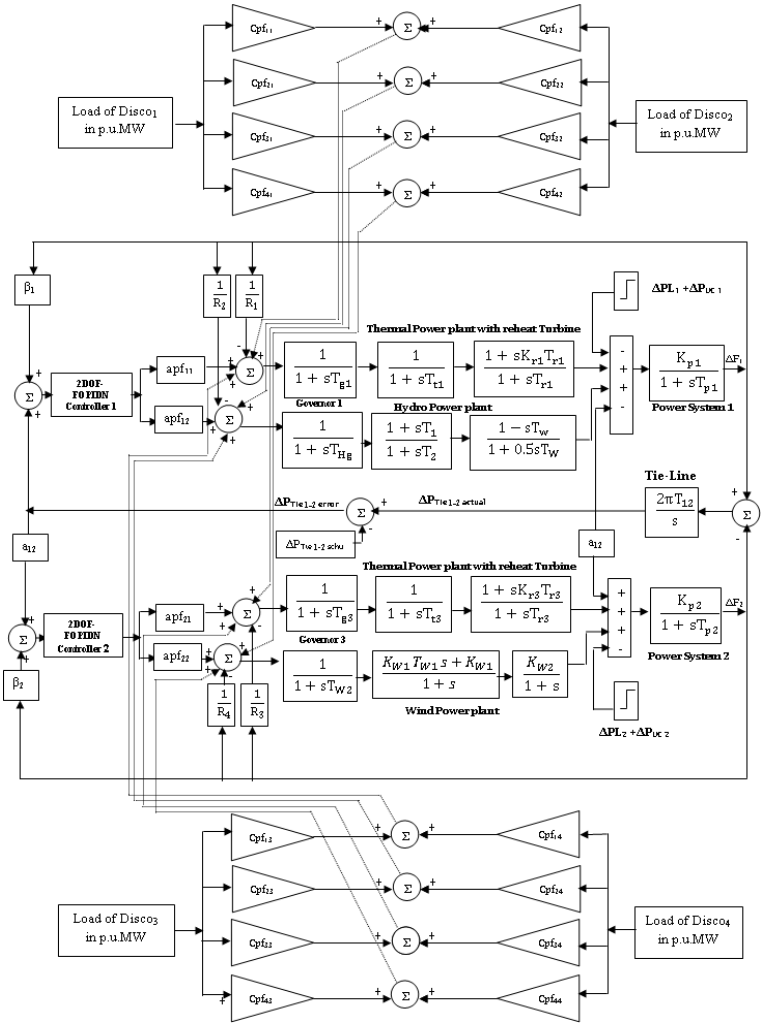

Fig 5: Transfer function of 2DOF-FOPIDN controller based AGC for two-area thermal-hydro-wind restructured power system

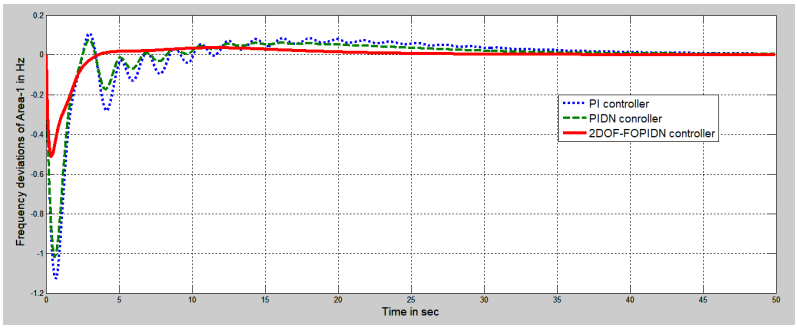

Fig. 6(a) Change in frequency deviations of area 1

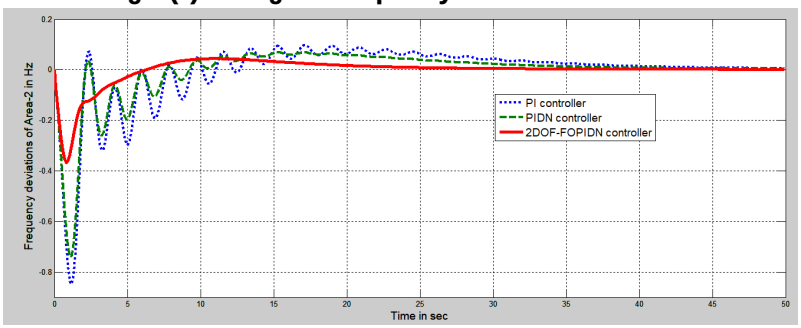

Fig. 6(b) Change in frequency deviations of area 2

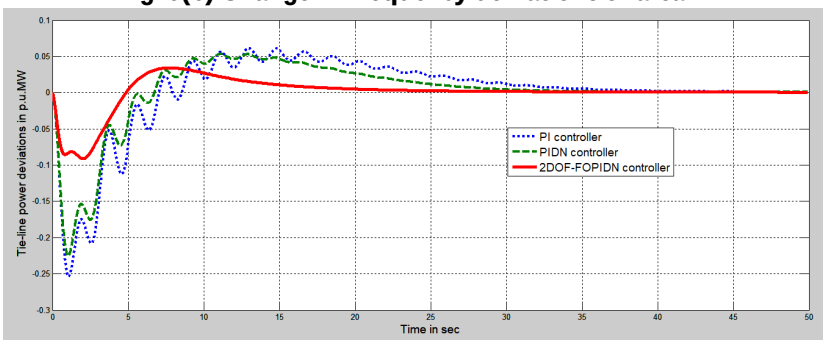

Fig. 6(c) Change in Tie-line power deviations (actual)

Fig.6. Comparison of dynamic responses of the change in frequency deviations and tie-line power deviations for the test system using proposed controllers under Poolco based transactions

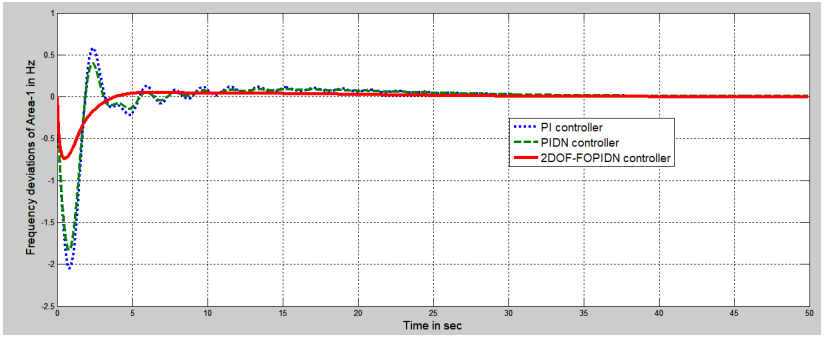

Fig. 7(a) Change in frequency deviations of area 1

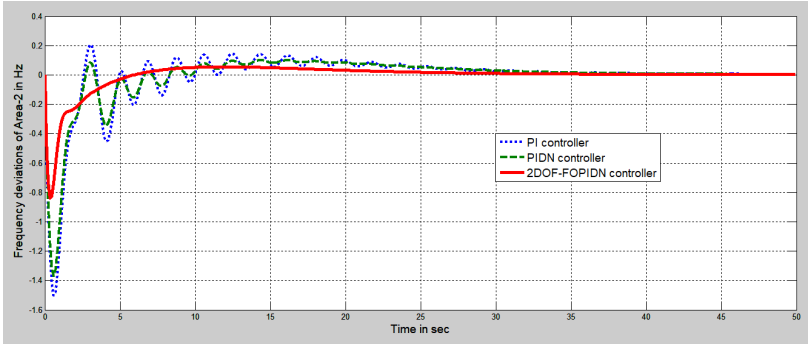

Fig. 7(b) Change in frequency deviations of area 2

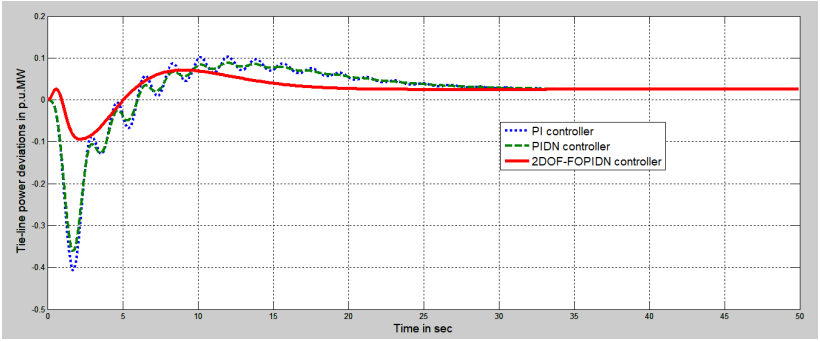

Fig. 7(c) Change in Tie-line power deviations (actual)

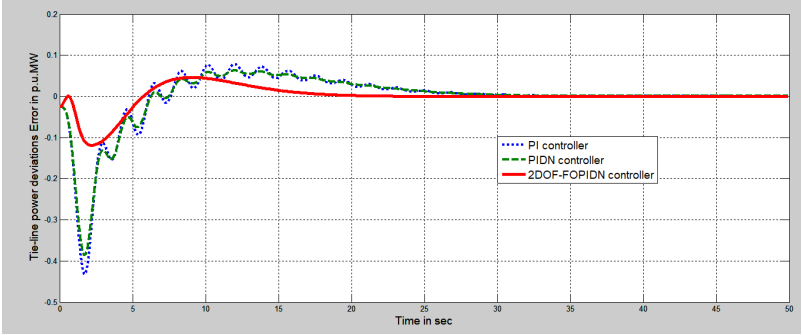

Fig. 7(d) Change in Tie-line power deviations (error)

Fig.7 Comparison of dynamic responses of the change in frequency deviations and tie-line power deviations for the test system using proposed controllers under bilateral based transactions

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RESEARCH ARTICLE

Cascade Multilevel Inverter with Reduced Harmonic Distortion for Renewable Energy Application

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ABSTRACT

In recent years the user demand gets increase with respect to its trend on environment. The Fossil fuel based power generation system can't handle the user demands in single hand manner. The Main objective of this paper is to develop an effective power quality of grid. This Grid is connected with photovoltaic power system via cascade H-bridge multilevel inverter. The Process of this system is carried out with MATLAB software. The Performance of system is recorded at different operating conditions. Then the recorded THD values of system are made to comparison in order to establish proposed system efficiency.

Keywords: power quality, grid, photovoltaic power, H-bridge, multilevel inverter, THD

INTRODUCTION

In Advanced photovoltaic cells or inverters, power plants can be connected to grid in direct manner [1]. So system can be enclosed with maximum power and voltage levels [2] [3].A Modular multilevel inverter provides an effective overall performance on various performance parameters. The Demand of system are in peak with rising population

of users. The Smart grid makes the designer to control at central location [4]. The Smart grids are improved to advanced form known as micro grid [5]. The Micro grid can produce energy by itself for each user. The Micro grid utilizes the energies produced by the renewable sources. The Micro grids can withstand upto 10KW energy [6]. An inverter has been utilized to integrate micro grids blocks for direct current to alternate current conversion. The Residential micro grids can be placed as individual manner or it will be connected with a PV grid. The PV inverters can be accessed with single or three phase connections [7]. The PV inverter grasps high power from the PV blocks. When it is connected with grid, it passes sinusoidal currents. The Inverters powers are categorized based on their power stages, capacitors placements and usage or absence transformer. By this effective power utilization can be achieved.

PHOTOVOLTAIC SYSTEMS

The Photovoltaic systems are enclosed with several number of inter linked blocks. These blocks helps to achieve certain performance level ratings. The Power supply design plays vital role. Each block in this grid system are powered based on the blocks requirement level. The Photovoltaic systems are classified based on their blocks and user demands. Figure 1 represents the Classification of PV systems [8]

PV module

The Solar cell connections are connected with respect to application requirements [9]. A Series string of cells (approximately 36 or 72) are utilized to obtain effective output voltage. A Complete package of entire blocks design is said to be module. This Prevents each cells from external environment factors such weather, dust etc [10]. Multiple cells are connected in series connection and sometimes in parallel connection as well. Figure 2 represents PV module structure with 36 cells in a series connection. All cells in the system will achieve same current. The Output voltage at module terminals will be the sum of each cell voltages. The String series of cells determines power for the entire system. In parallel connection system current will be sum of each cell and the output voltage at module terminals will be equal to a single cell.

Array

An Array is defined as a structure of PV module structure with 36 cells fabricated on the same plane with proper power supply with respect to the applications. Arrays can with stand power capacity between 100w to 100kw. The Single module cells connection is similar to connection given for modules in an array. For high level voltage, modules will be in series connection. Similarly, for high current they will be in parallel connection [11-12]. The Array structure in figure 3 consists of four parallel connections of four module strings in a series connection.

The Voltage for n modules in series connection is expressed as:

$$V_{series} = \sum_{j=1}^{n} V_j = V_1 + V_2 + ... + V_n \quad for \quad I > 0 \qquad (1)$$

$$V_{seriesOC} = \sum_{j=1}^{n} V_j = V_{oc1} + V_{oc2} + ... + V_{ocn} \quad for \quad I = 0 \qquad (2)$$

The Current and voltage for m modules in parallel connection is expressed as:

$$I_{parallel} = \sum_{j=1}^{n} I_j = I_1 + I_2 + ... + I_m \qquad (3)$$

$$V_{parallel} = \sum_{j=1}^{n} V_j = V_1 = V_2 = ... = V_m \qquad (4)$$

The Array connection of modules has to be in a proper connection. So that effective performance can be obtained from system. If not it leads to noises, heat and malfunctions etc. The Bypass diode prevents the failure issues in connection terminals. The Bypass diode in a system leads to high cost in design. If the bypass diode gets damages replacement will be crucial at the moment.

Grid connected systems

Grid connected PV systems can standalone with its own requirements of energy [13]. In 2004, grids implementation for a systems gets increased in Germany about 1 GW. [14]. The Failure issues in PV system connections for utilizing grid are solved with IEEE standard 929-2000 in 2000 [15]. The Standard integration was made on PV systems for power networks are revealed at 2 major categories namely,1) Safety and 2) Power quality. The IEEE Standard 929 reveals that it has limitation on PV systems mainly on total harmonic distortion at the point of common coupling (PCC) with Clause 10 of IEEE Std 519-1992.

The Limits will be applicable upto 6 pulse converters. In normal distortion cases, if pulse counts are above 6 it has to undergo with certain conversions [16]. The Distortion limits are listed in Table 1. The Issue of islanding is defined as inverter will get turns off automatically when the power source gets absent from the network. If it does not occurs the safety of staff and common people has to meet consequences. Radio frequency suppression also needs effective shield and filters.

CONVENTIONAL CASCADE H BRIDGE

A Multilevel inverter with direct current source within H- bridge cells has series connection [17]. Each cell encloses an individual DC source. It also has 2 branches in a parallel connection. Where each branch has 2 switches (complement to each other) [18-20]. The Second branch alignment has been utilized for the switch implementation. Based on cells counts the output voltage level can be determined. Figure 6 represents a single cell with 3 parameters namely, -Vdc, 0, Vdc [21-23]. For obtaining maximum output voltage level, a cells count in a system has to larger in amount.

$$m = 2n + 1 \quad (5)$$

Where, n denotes the number of H –bridge; m denotes the number of levels

NEW 21 LEVEL CASCADE H-BRIDGE MULTILEVEL INVERTER FOR PV SYSTEM

The Inverter is utilized for converting DC electrical energy into an AC electrical energy. The Inverter plays major role in conventional energy sources connected with grids. The Principle of DC-DC rectifiers and inverters are same at its control units. The Proposed 21 level inverter contains of two parts namely, 1) Level marker and 2) H- bridge. The Level marker has 10 DC sources and 20 switches. If switches and DC source are set then the voltage levels gets generated. The Output voltage polarity will be limited by H-bridge part. So that H-bridge alters the polarity of switches (S1, S2) performed at positive half cycle when (S3, S4) switches are performed at negative half cycle. The MOSFETs trigger pulses are processed with respect to pulse generators. Figure 8 represents the proposed multilevel inverter with 21 level output voltage. Figure 9 represents THD values of 21 levels inverter. The Proposed multilevel inverter consists of minimum number of switches when compared with conventional cascade inverter. The Proposed multilevel inverter can be further updated to high level output voltage with support of equations expressed below:

$$N_{levvel} = 2n+1$$
$$N_{switch} = 2n+3$$
$$N_{o\max} = 2n \quad (6)$$

Where, n denotes the number of DC sources.
N_{level} denotes the number of output voltage levels.
N_{switch} denotes the number of switches.
V_{omax} denotes the maximum output voltage.

RESULT AND DISCUSSION

The Proposed multi level inverter for PV power system has been carried out using MATLAB/SIMULINK software. The Proposed multi level inverter efficiency has been compared with traditional inverter designs [24-25], When off-grid was performed on load (RL). Figure.10 (a) represents the PV Module Characteristic Curve of I-V curve. Figure.10 (b) represents the PV Module Characteristic Curve of P-V Curve. Figure.11 represents the output voltage waveforms of proposed inverter. Figure.12 represents output current waveforms of proposed inverter. In load terminal, post filtering output voltage waveform and output current waveforms are in sinusoidal form. In Pre-filtering, the output voltage waveforms are in quasi sinusoidal form. Figure.13 (a) and Figure.13 (b) represents the harmonic order of the output. The Output voltage THD was observed to be 13.5%. At these states the output current THD was also 1.34%. The Simulation was executed upto 0.08 s for obtaining operations 4 cycles. The Table 2 compares the proposed TCHB with different inverter topologies with load (RL) and THD parameters.

CONCLUSION

In this paper, multilevel inverter topology is implemented. The Relationships of photovoltaic systems is analyzed and simulated with Matlab software. The Proposed 21-level cascaded inverter has been designed for renewable energy applications. The Improvement of power stability and power quality in voltage source and current source, THD values are recorded then analyzed with existing design represented in Table 1. The Proposed inverter was obtained with reduced voltage THD of 13.5 % and reduced current THD of 1.34 %. From these results it has been proved that proposed inverter design provides reduced THD. In conclusion, based on evaluation results the proposed 21 level inverter is recommended for photovoltaic power system. In future efficient multilevel inverter can be developed with reduced components.

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Table 1: Distortion limits as recommended in IEEE Std 519-1992 for six-pulse converters

Odd harmonics	Distortion limit
3rd – 9th	< 4%
11th – 15th	< 2%
17th – 21st	< 1.5%
23rd – 33rd	< 0.6%
above 33rd	< 0.3%

Table 2. Total Harmonic Distortion(THD) Comparison

Inverter Topology	Level	Voltage THD %	Current THD %
Design 1 [24]	23	4.23	2.74
TCHB [25]	9	15	2.57
Proposed Inverter	21	13.5	1.34

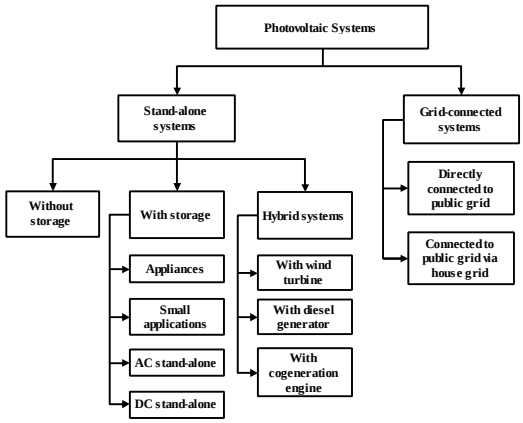

Figure.1: Classification of PV systems

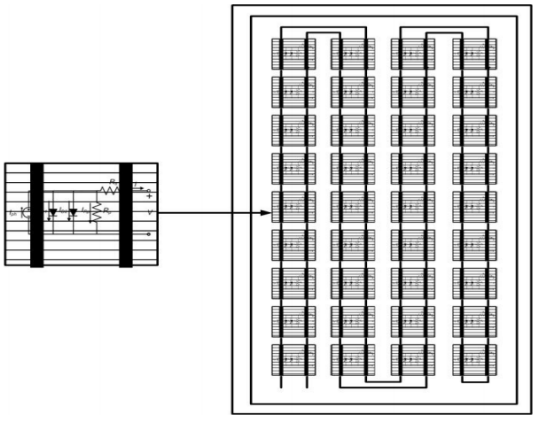

Figure 2: Structure of a PV module with 36 cells connected in series

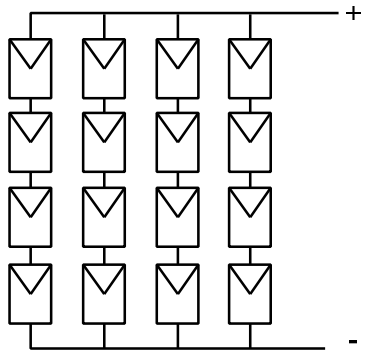

Figure 3: Structure of a PV array

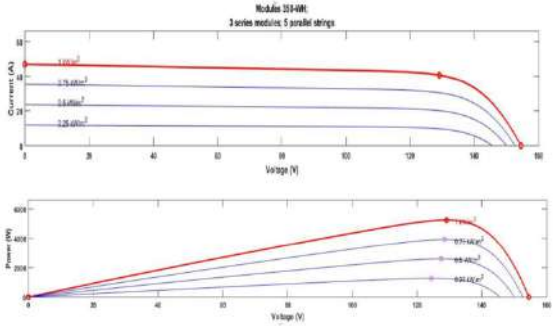

Figure 4. Photovoltaic array VI characterises

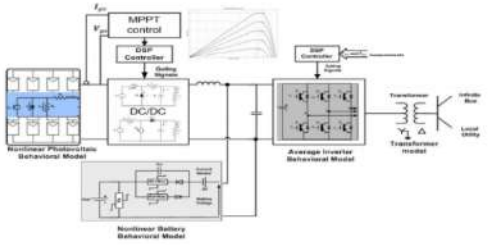

Figure 5: Grid connected PV system

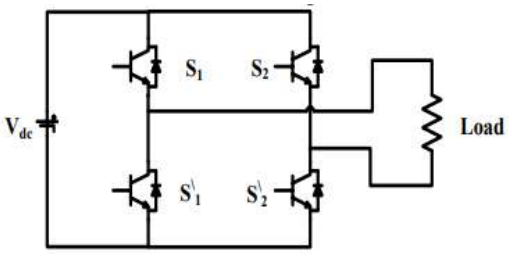

Figure 6: single cell conventional cascade three level

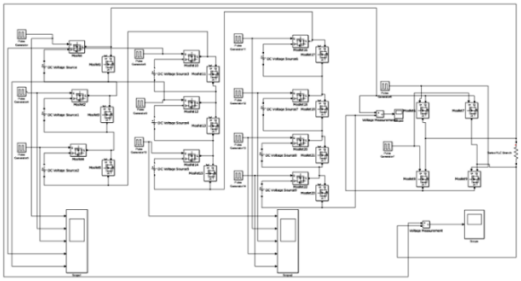

Figure 7. Simulation of 21 level inverter for PV power system

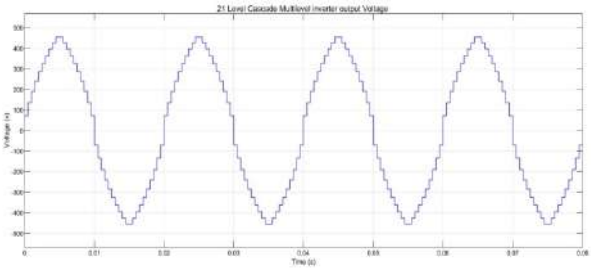

Figure 8. 21 levels inverter for PV power system output voltage waveform

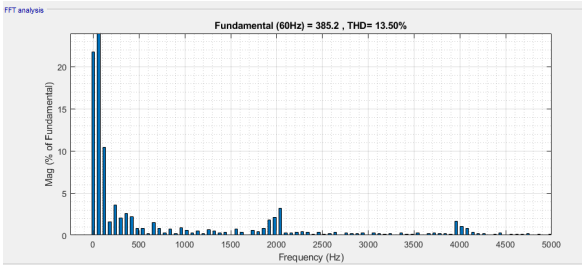

Figure 9. THD of 21 levels inverter for PV Power system

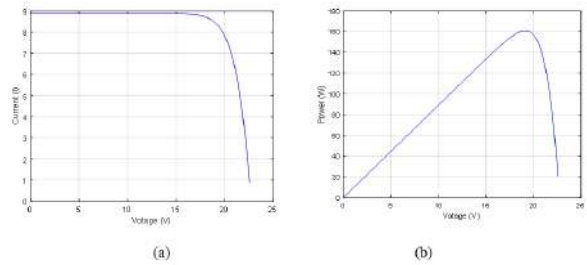

Fig. 10. PV Module Characteristic Curves (a) I-V curve (b) P-V Curve

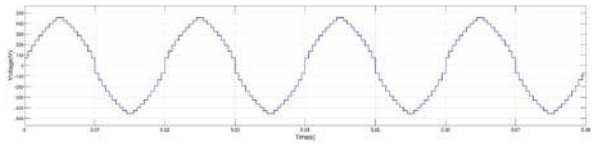

Figure 11. PV integration of Distributed grid voltage waveform

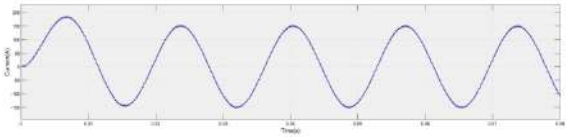

Figure 12. PV integration of Distributed grid current waveform

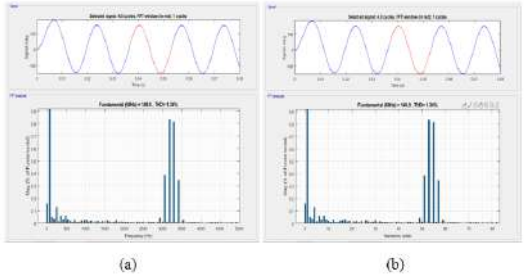

Fig. 13. Output-Current and Voltage Results. (a) FFT analysis with frequency, (b) FFT analysis with harmonic order

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REVIEW ARTICLE

Neuroprotective Effects of Spices and Fruits- A Review

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ABSTRACT

Fruits and spices have been used for generations by humans as part of the food and to treat different ailments even though we don't often consume these are in large quantities. Small doses of the same can be powerful providers of nutrients, vitamins, minerals antioxidants, anti-inflammatory, neuroprotective and cancer-fighting constituents. The active phytochemicals present in the fruits and spices provide the molecular basis for these actions. Spices have a wide variety of bio functions and their additive or synergistic actions are likely to protect the human body against a variety of insults, further which as a part of the diet have a holistic effect on human health. Vitamins and minerals present in Fruits can function as antioxidants, anti-inflammatory agents and phytoestrogens. Neuroprotection is the restoring of structure and function of neurons from various insults arising from cellular damages induced by a variety of neurodegenerative diseases and agents, so in this review we deal with spices and fruits used in medicines and diets, focusing on their neuroprotective active components, emphasis will be placed on the antioxidant and anti-inflammatory activity exerted by specific molecules present in spices and fruits.

Keywords : Spice, fruits,Neuroprotective,antioxidants, Neurodegeneration.

INTRODUCTION

For primary health care, most of the population depends on traditional medicine. In recent years, growing attention has been focused on traditional medicine and in that, a large number of plants have been used to cure neurodegenerative diseases. People with Nervous disorders like epilepsy are severely affected by health-related problems and discrimination and also have affect on their movement, speaking, mood, breathing, and memory. Taking into consideration of the existing knowledge on the medicinal plants for the treatment of neurologic disorders, more research in the area of ethnomedicine and ethnopharmacology is required. The spices and fruits which were used traditionally for dietary, food additive, and various medicinal purposes having carotenoids, monoterpenes, and polyphenols which enhanced neural functions. These increases and decreases antioxidant and oxidant level respectively. Furthermore, neuroprotective of plants occurs via reduced proinflammatory cytokines such as IL-6, IL-1b, TNF-a, and total nitrite generation. Therefore the accumulated evidence suggests that naturally occurring phytocompounds in fruits, spices, and nuts may potentially hinder neurodegeneration and improve memory and cognitive function.

NEUROPROTECTIVE SPICES

Crocus sativus

Crocus sativus L (*C. sativus*), commonly known as saffron belongs to the Iridaceous family, Crocoideae superfamily which is cultivated in many countries including Iran, Afghanistan, Turkey, and Spain. Saffron consists of dried and dark-red stigma with a small portion of the yellowish style attached of *C. sativus.* It is used mainly as herbal medicine in various regions of the world. 150 different compounds including carbohydrates, polypeptides, lipids, minerals, and vitamins were found in Saffron. Crocin, the chief active ingredient of saffron, is a family of red-colored and water-soluble carotenoids, which are all glycosides of crocetin. Another constituent of saffron was Picrocrocin which has a bitter taste [1].

Neuroprotective effects of *C. sativus*

In traditional medicine, *Crocus sativus* is used to treat cognitive disorders. Recently constituents of *C. sativus* were used to treat some neural disorders and to relax smooth muscle. The data obtained from a current study provide insight into the efficiency of saffron in reducing neural damage. The study reveals that the prevention of oxidative stress, down-regulation of apoptotic proteins caspase-3 and Bax, as well as exertion of a vascular protective role by reducing NO and BNP, are among the main mechanisms that mediate the neuroprotective effect of saffron. Moreover, this study reveals the modulation of VEGF by saffron is another mechanism arbitrating its neuroprotective and antiapoptotic potential. As a result, it can be concluded that saffron supplementation could provide a favorable strategy to protect against ischemia/reperfusion in brain injury [2]. In another study explored the neuroprotective effects of saffron on the late cerebral ischemia in rats., inflammatory cytokine contents were detected by Western blotting and ELISA methods. Saffron improved body weight loss, neurological deficit, and spontaneous activity. Also reduced anxiety-like state and cognitive dysfunction, which were detected by marble-burying test (MBT), elevated plus maze (EPM), and novel object recognition test [3].

Nigella sativa

Nigella sativa L. (*N. sativa*) is an annual herbaceous plant belonging to the Ranunculaceae family, widely grown in the Mediterranean countries, Western Asia, Middle East, and Eastern Europe. Seeds of N. sativa have been added as a spice to a variety of Persian foods such as pickle, sauces, bread, and salads[4]. Chemical components of *N.sativa* seeds include oil, protein, carbohydrate, and fiber. The fixed oil chemical compositions of N. sativa are linoleic acid, oleic acid, Palmitic acid, Arachidic acid, Eicosadienoic acid, Stearic acid, Linoleic acid, and Myristic acid5. The major phenolic compounds of N. sativa seeds are p-cymene(37.3%), Thymoquinone (TQ) (13.7%), carvacrol (11.77%), and thymol (0.33%) [4,5,6].

Neuroprotective effects *N. sativa*

In a recent study unilateral intrastriatal 6-hydroxydopamine (6-OHDA)-lesioned rats were daily pretreated p.o. with Thymoquinone, three times at an interval of 24 h. After 1 week, there observed a reduction in the number of neurons on the left side of the substantia nigra pars compacta (SNC), malondialdehyde (MDA) and increased nitrite level in midbrain homogenate and activity of superoxide dismutase (SOD) reduced. Pretreatment of Thymoquinone improved turning behavior, prevented the loss of SNC neurons, and reduced the level of MDA. Results suggest that TQ could afford neuroprotection against 6-OHDA neurotoxicity and this; along with other therapies it may provide benefits, in neurodegenerative disorders including parkinsonism [8]. Furthermore, N. sativa improved scopolamine-induced learning and memory impairment as well as reduced the AChE activity and oxidative stress of the rat brain [9].

Coriander sativum

Coriander (*Coriandrum sativum* L.), is the herb belonging to parsley family (Apiaceae). Chief active constituents of *Coriandrum sativum* are fatty oils and essential oils. The major component of which is S-(+)-linalool (60-70%) other minor active constituents in essential oil are monoterpenes hydrocarbons viz. α-pinene, limpnene, γ- terpinene, p-cymene, borneol, citronellol, camphor, geraniol and geraniol acetate, heterocyclic components like pyrazine, pyridine, thiazole, furan and tetrahudrofuran derivatives, isocoumarins, coriandrin, dihydrocoriandrin, coriandrons A-E, flavonoids, pthalides, neochidilide, digustilide phenolic acids and sterols [10].

Neuroprotective effects *C. sativum*

Researches revealed that Oral administration of hydroalcoholic extract of coriander sativum(CHA) considerably attenuated hyperglycemia and decreased pain threshold in diabetic rats therefore it is predicted that CHA might be beneficial in diabetes-induced neuropathic pain by inhibiting oxidative/nitrosative stress and inflammatory cytokine [11]. Another study investigated that continuous oral administration of *Coriandrum sativum* seed extract for 12 weeks can make better aging-induced memory loss in the senescence-accelerated SAMP8 mouse model [12].

Ferula assafoetida

Ferula assafoetida, commonly called as asafoetida, is the gum oleoresin exuded from the tap root of several species of Ferula. It is a monoecious, herbaceous, perennial plant of the family Apiaceae, is also known as devil's dung, giant fennel, stinking gum, or hing. *F.Assafoetida* is native to central Asia, eastern Iran to Afghanistan. The plant grows to 2 m (6.6 ft.) tall and is not harvested until four years old [13]. E-1-propyl sec-butyl disulfide is a major component, and 25compounds were identified in the hydro distilled oil. E-1-propenylsec-butyl disulfide (40.0%) and germacrene B (7.8%) are the major components of Ferula assafoetida [14].

Neuroprotective effects *F. assafoetida*

Retrieval of motor and sensory functions on a sciatic nerve injury induced mouse model studied, and the findings indicated that administration of *Ferula asafoetida* results in fast functional recovery from mechanically induced insult and this improvement may be due to the antioxidant property of the plant [15]. Research study showed that oleo gum resin of *F. asafoetida* can enhance regeneration and re-infiltration in the neuropathic tissue in mice; therefore it acts as a neuroprotective and nerve simulative agent in peripheral neuropathy [16]. Scientific evidence has also shown that *F. asafoetida* resin can potentially inhibit monoamine oxidase B (MAO-B) and it can be used in the therapy of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases [17].

Thymus vulgaris

Thyme is a small shrub belonging to the family lamiaceae the stems become woody with age. The leaves can be oval or rectangular in shape and fleshy aerial parts are used for the production of volatile oil mainly by steam distillation [18]. The major compounds found in *T. vulgaris* were thymol and o-cymene, with the major components being oxygenated monoterpenes and monoterpene hydrocarbons [19].

Neuroprotective effects of *T. vulgaris*

A recent work investigated the effect of *Thymus vulgaris* L. essential oil on the enhancement of cognitive function via the action on cholinergic neurons using scopolamine (Sco)-induced zebrafish (Danio rerio) model of memory impairments. The results suggest that *T. vulgaris* essential oil (TEO) may have preventive and/or therapeutic potentials in the management of memory deficits and brain oxidative stress in zebrafish with amnesia [20]. Another study showed protective effects of thymol in ROT-induced neurotoxicity and neurodegeneration in Wistar rats, mediated by the preservation of endogenous antioxidant defense networks and attenuation of inflammatory mediators including cytokines and enzymes [21]. Researchers have reported that *Thymus vulgaris* extract has a neuroprotective activity; Mechanisms of neuroprotective action might be associated with antioxidant activity and inhibition of oxidative stress [22]. Effect of *Thymus vulgaris* (*T. vulgaris*) on learning and memory functions in scopolamine-induced memory deficit in rats also reported, administration of *T. vulgaris* extract significantly preserved memory and learning impairments induced by scopolamine [23].

Zataria multifloria

Zataria multiflora (ZM) is a thyme-like plant belonging to the Lamiaceae family that grows wild only in Iran, Pakistan, and Afghanistan. It has used traditionally as a diaphoretic, diuretic, anesthetic, antiseptic, carminative, stimulant, and anti-spasmodic and analgesic. There are 56 compounds were identified in *Z. multiflora* essential oil, of which the major constituents are carvacrol, linalool thymol, and p-cymene [24].

Neuroprotective effects of *Z. multiflora*

The effects of hydroalcoholic extract of (*Z. multiflora*) on memory changes, as well as inhaled paraqut (PQ) lung injury in rat, were determined and the results suggest that *Z.* multiflora treatment improved learning and memory impairment as well as lung inflammation and oxidative stress induced by inhaled PQ [25]. another research study poved the plausible effects and related mechanisms of *Zataria multiflora* Essential Oil (ZMEO) against memory impairment in a rat model of the Alzeimires disease and concluded that ZMEO has a protective effect against memory impairment in rats with AD at least partly via reducing hippocampal AchE activity and enhancement of BDNF levels without a change in antioxidant status [26].

Curcuma longa

Curcuma longa L. belongs to family Zingiberaceae which is one of the oldest cultivated spice plants in the south-east Asian countries. Curcumin the active substance of turmeric possesses multiple therapeutic properties. In recent years, much detailed research both in vitro and in vivo along with clinical studies revealed that it has got various biological activities related to its, antioxidant, anti-inflammatory and cancer-preventive properties. It has been stated at the molecular level, that curcumin prevents cell proliferation, metastasis creation, and apoptosis. Recent study shown that curcumin can block TNF-s, they are the main mediators of most inflammation-related diseases [27].

Neuroprotective effects of *C. longa*

Recent study suggested that curcumin reduced inflammation, oxidative damage and cognitive deficits in rats receiving CNS infusions of toxic Aβ [8]. Since curcumin is structurally similar to the amyloid-binding dye Congo red, it has the potential to bind with amyloid and inhibit Aβ aggregation and thus blocked Aβ aggregations dose-dependently [28]. Some researches proved that curcumin can reduce the α-synuclein aggregation23 and administration to cultured cells with α-synuclein aggregate formation results in lesser aggregates. Thus, these data provide some rationale relevant to curcumin-induced neuroprotection suggesting that it might protect from Parkinson's disease (PD) [29]. Researchers also evaluated possible beneficial effects of curcumin in epilepsy, Curcumin, in a dose-dependent manner, reduced MDA and increased GSH levels in the brain tissue of PTZ -kindled mice [30]. It also reduced the kainic acid-induced hippocampal cell death in mice [31]. In recent studies have shown that curcumin can cross the blood-brain barrier and can have a neuroprotective effect in cerebral ischemia-reperfusion (I/R) injury [32, 33].

NEUROPROTECTIVE FRUITS

Blueberry

Blueberry is a species from the family Ericaceae. Fruits are rich in anthocyanins and these anthocyanine pigments gives red, blue, and purple coloration to ripe berries. Anthocyanin amount increases greatly in ripening season there by it is much easier to differentiate between early to fully ripe fruit. In ripe blueberries about 60% of the total polyphenolics is Anthocyanin flavonoids and the major health benefits of blueberry contributed by anthocyanins. Polyphenolic compounds in Blueberry include both nonflavonoid and flavonoid types. Hydroxycinnamic acid esters especially chlorogenic acid is the nonflavonoid polyphenolic compounds present in blueberries [34].

Neuroprotective effects of Blueberry

Many of the researches reported that blueberries have ability to restore memory and cognitive deficits in the brain. Preclinical research reports showed that supplementation of bluberry is associated with enhanced memory and motor performance in aged animals [35,36]. A recent study showed that blueberry anthocyanins may have a protective effect against perfluorooctane sulfonate (PFOS) induced neurotoxicity and DNA damage [37]. These fruits are also capable of modulating signaling pathways involved in, neurotransmission, cell survival, inflammation, and enhancing neuroplasticity. The neuroprotective potential of berry fruits is due to the presence of phytochemicals present such as catechin, quercetin, anthocyanin, kaempferol, caffeic acid, and tannin [38]. Research studies also suggest that short-term blueberry administration may improve heat shock protein 70 (HSP70) mediated protection against numerous neurodegenerative processes in the brain [39].

Mulberry

Mulberry (*Morus alba L.*) belonging to the Moraceae family is also known as Sangzhi or *Ramulus Mori.* Mulberry is native to China, but it also cultivated in many parts of the world including Africa, America Asia, and Europe. In Chinese traditional Medicine, mulberry fruits are used to enhance eyesight and protect liver damage Mulberry also has been used traditionally to treat diabetes and premature white hair [40]. The most important constituent of mulberry fruits are anthocyanins which are responsible for the color attribute and biological activities such as antioxidant, antimicrobial, and neuroprotective, anti-inflammatory properties [41].

Neuroprotective effects of Mulberry

Researchers showed that mulberry fruit extract, by its anti-apoptotic and antioxidant effects, significantly protect neurons against neurotoxins in *in-vitro* and *in vivo* Parkinson's disease (PD) models. These results suggest that for treating or preventing PD, mulberry fruit or its compounds can be used as potential neuroprotective candidates [42]. Another research showed that mulberry fruit extract enhances hippocampal plasticity and memory impairment in an animal model of experimental menopause with metabolic syndrome, thereby that can be used as neuroprotectant and memory enhancer for menopausal women with metabolic syndrome [43]. Investigatations also proved that Mulberry fruit extract protects neuronal cells against oxidative stress-induced apoptosis through upregulating the expression of BDNF(brain-derived neurotrophic factor) and antioxidant enzymes by stabilizing the activation of the TrkB/Akt (tropomyosin-related kinase receptor) pathway [44].

Strawberry

The strawberry tree (Arbutus unedo) is a shrub, which is prevalent in most of Europe. It comes under the Ericeae family [45]. Polyphenol compounds that present in ripe strawberries include flavonoids, comprising anthocyanins, flavonols, and flavan-3-ols, as well as phenolic acids and ellagitannins. The anthocyanins consist of four main compounds; pelargonidin-3-*O*-glucoside, pelargonidin-3-*O*-malonylglucoside, and, to a lesser extent, pelargonidin-3-*O*-rutinoside, and cyanidin-3-*O*-glucoside [46].

Neuroprotective effects of Strawberry

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease resulting from the death of motor neurons in the brain, brain stem, and spinal cord and researches proved that anthocyanin-enriched extract from strawberries have significant potential as therapeutic agents in a preclinical model of ALS because of their capability to decrease astrogliosis in the spinal cord and preserve neuromuscular integrity and muscle function. Thus, these unique compounds may provide therapeutic benefits for the treatment of ALS [47]. Oxidative stress due to Aβ protein is one of the major reasons for the pathogenesis of Alzheimer s disease [48]. Researchers evaluated the anti-oxidative effect of strawberries in Hydrogen peroxide (H_2O_2) induced neurotoxicity in PC12 cells and viability of cell was determined using the LDH assay. It was found that Pre-treatment with anthocyanin-rich strawberry extract showed improved cell viability in H_2O_2 induced neurotoxicity-induced PC12 cells [49].

Pomegranate

Pomegranate (*Punica granatum*) is a fruit-bearing deciduous shrub belonging to the family Lythraceae, It has been used for thousands of years to cure a wide range of diseases, also has great nutritional values and numerous health benefits. Pomegranate has been used in traditional medicine to treat digestive disorders, skin disorders, arthritis, sore throats, coughs, urinary infections, and to expel tapeworms. Recent research also reveals that pomegranates might be useful in treating serious conditions such as skin cancer, prostate cancer, osteoarthritis, and diabetes [50]. The pomegranate fruit is a rich source of ellagitannins (ETs) such as punicalagin, punicalin, pedunculagin, gallic and ellagic acid esters of glucose, and ellagic acid (EA), which contribute to the antioxidative, anti-inflammatory, and anti-apoptotic activity of pomegranate [51].

Neuroprotective effects of Pomegranate

A recent study examined the capability of pomegranate juice for protection against Parkinson's disease (PD) in a rat model (Parkinsonism induced by rotenone). The results of the study indicated that treatment with pomegranate juice prevents PD-like features in rats [51]. Researchers proved that Pomegranate Juice Extracts protect against the neurotoxic effects of 1-Methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (an environmental toxin) in humans neurons [52]. Another study found that urolithins present in pomegranate contribute to pomegranate's anti- Alzheimer's disease effects [53]. Research results also shown that pomegranate juice has a neuroprotective effect against Alzheimer's-like disease induced by aluminum chloride [54].

Papaya

Papaya belongs to a small family Caricaceae having four genera in the world, of which *Carica papaya* L. is the most widely cultivated and the best-known species [55]. The pulp composition comprises vitamins A, C, E, and B complex vitamins (pantothenic acid and folate,) minerals such as magnesium and potassium, as well as food fibers. Besides these nutrients, papaya contains the enzyme papain, effective in increasing intestinal motility and transit time, and is also utilized in the treatment of traumas and allergies. Some studies observed the presence of proteolytic enzymes, such as chymopapain, with anti-viral, antifungal, and antibacterial properties [56].

Neuroprotective effects of Papaya

Nuclear factor erythroid 2-related factor (Nrf2) in astrocyte plays important role in brain homeostasis and a study on Fermented papaya preparation (FPP) has shown that it has got anti-oxidative, anti-inflammatory, and immunoregulatory properties, experimental results indicated that FPP enhances the anti-oxidative capacity by the activation of Nrf2 in astrocytes, revealing it can provide neuroprotection in oxidative stress-related neurodegenerative diseases [57]. The neuroprotective effects of ripe aqueous extract of *Carica papaya* on the traumatized cerebral cortex of Wistar rats were studied Carica papaya fruit extracts appeared to protect the brain against Traumatic brain injury, induced oxidative stress [58].

Apple

Apple (*Malus domestica*) belongs to the Rosaceae family. Fat content is very low in apple and contains carbohydrates (fructose is the dominant one) vitamins (especially vitamin C), minerals (potassium and magnesium), triterpenoids (ursolic acid), dietary fiber (soluble and insoluble), and polyphenols [59].

Neuroprotective effects of Apple

Experimental studies have shown administration of apple polyphenol extract significantly improved memory retention, attenuated oxidative damage, acetylcholinesterase activity, and aluminum (Al)level in Al treated rats [60]. Studies also suggested that Apple polyphenols improved significantly chronic ethanol-induced memory impairment and the hippocampal CA1 neurons damage [61]. Apple cider vinegar (ACV), an acidic solution usually obtained from apple's fermentation, is rich in polyphenols; researches showed that ACV attenuated LPS-induced anxiety- and depressive-like behaviors in mice. Co administration of Apple juice concentrate with drinking water maintains acetylcholine which shows that the consumption of antioxidant-rich foods such as apples can prevent the decline in cognitive performance that accompanied by dietary, genetic deficiencies and aging [62].

CONCLUSION

Nutritional therapy in neurodegenerative diseases is the best alternative healing therapy using nutraceuticals and functional foods as therapeutics. This is based on the assumption that food is not only a source of nutrients and energy givers but also have neuroprotective potentials too. Therefore, consumption of plant foods is thus not only a source of nutrients and energy but can also provide health benefits beyond basic nutritional functions. Above-mentioned Spices and fruits are very good sources of different kinds of molecules which help improve human health, further many of them have been reported to exert neuroprotective effects in various experimental models. These findings suggest that the consumption of spices and fruits has potential in the prevention of neurodegenerative diseases as they are the natural sources of antioxidant, antimicrobial, and enzyme inhibitory agents.

CONFLICTS OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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RESEARCH ARTICLE

Characterizations of Some ω-Open Sets in Ideal Topological Spaces

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ABSTRACT

We make provided a new category of the concepts of α-$\mathcal{I}_\omega$-open sets and β-$\mathcal{I}_\omega$-open sets were studied in detail. We introduce and investigate the new concept called semi-$\mathcal{I}_\omega$-open sets which is weaker than α-$\mathcal{I}_\omega$-open sets and stronger than β-$\mathcal{I}_\omega$-open sets. Also we introduce and investigate some new generalized classes of related to the ideal space in this paper.

Keywords: Topological, $\boldsymbol{\omega}$, open sets, Spaces

INTRODUCTION AND PRELIMINARIES

An ideal $\mathcal{I}$ [22] on a topological space (X, τ) is a non-empty collection of subsets of X which satisfies the following conditions.

1. $B \in \mathcal{I}$ and $A \subset B$ imply $A \in \mathcal{I}$ and
2. $B \in \mathcal{I}$ and $A \in \mathcal{I}$ imply $B \cup A \in \mathcal{I}$.

Given a topological space (X, τ) with an ideal $\mathcal{I}$ on X if $\mathbb{P}(X)$ is the set of all subsets of X, a set operator $(.)^\star: \mathbb{P}(X) \to \mathbb{P}(X)$, called a local function of A with respect to τ and $\mathcal{I}$ is defined as follows: for $A \subset X$, $A^\star(\mathcal{I}, \tau) = \{x \in X: M \cap A \notin \mathcal{I}$ for every $M \in \tau(x)\}$ where $\tau(x) = \{M \in \tau: x \in M\}$ [10]. A Kuratowski closure operator $Cl^\star(.)$ for a topology $\tau^\star(\mathcal{I}, \tau)$, called the $\star$-topology, finer than τ is defined by $Cl^\star(A) = A \cup A^\star(\mathcal{I}, \tau)$ [21]. We will simply write $A^\star$ for $A^\star(\mathcal{I}, \tau)$ and $\tau^\star$ for $\tau^\star(\mathcal{I}, \tau)$. If $\mathcal{I}$ is an ideal on X, then $(X, \tau, \mathcal{I})$ is called an ideal topological space or an ideal space. $Int^\star(A)$ will denote the interior of A in $(X, \tau^\star)$.

In 1982, the concepts of ω-closed sets and ω-open sets were introduced and studied by Hdeib [6]. In 2009, Noiri et al [15] introduced some generalizations of ω-open sets and investigated some properties of the sets. Moreover, they used them to obtain decompositions of continuity. The study of ideal topological spaces was initiated by Kuratowski [11]. Jankovic and Hamlett [8] developed the study in local and systematic fashion and offered some new results, improvements of known results, and some applications. Later, several authors studied ideal topological spaces by giving several convenient definitions.

In this paper, we introduce the concepts of α-$\mathcal{I}_\omega$-open sets and β-$\mathcal{I}_\omega$-open sets were studied in detail. We introduce and investigate the new concept called semi-$\mathcal{I}_\omega$-open sets which is weaker than α-$\mathcal{I}_\omega$-open sets and stronger than β-$\mathcal{I}_\omega$-open sets. Also we introduce and investigate some new generalized classes of related to the ideal space.

Definition 1.1 *[2] A topological space (X,τ) is called submaximal if every dense subset is open.*

Definition 1.2 *[16] A subset A of a topological space (X,τ) is said to be semi-ω-open if $A \subset Cl(Int_\omega(A))$.*

Definition 1.3 *[16] A subset A of a topological space (X,τ) is said to be*

1. semi *-ω-open if $A \subset Cl_\omega(Int(A))$.
2. semi *-ω-closed if $Int_\omega(Cl(A)) \subset A$.

Definition 1.4 *[8] A subset A of an ideal topological space $(X,\tau,\mathcal{I})$ is said to be $\star$-closed if $A^\star \subset A$ or $Cl^\star(A) = A$.*
The complement of an $\star$-closed set is called $\star$-open.

Lemma 1.5 *[8] Let $(X,\tau,\mathcal{I})$ be an ideal topological space and M, N subsets of X. Then the following properties hold:*

1. $M \subset N \Rightarrow M^\star \subset N^\star$,
2. $M^\star = Cl(M^\star) \subset Cl(M)$,
3. $M^\star \cup N^\star = (M \cup N)^\star$,
4. $(M^\star)^\star \subset M^\star$,
5. $M^\star$ is closed in (X,τ),
6. If $M \in \tau$, then $M \cap N^\star \subset (M \cap N)^\star$.

Definition 1.6 *[3] A subset A of an ideal topological space $(X,\tau,\mathcal{I})$ is called $\star$-dense if $Cl^\star(A) = X$.*

Definition 1.7 *[5] A subset A of an ideal topological space $(X,\tau,\mathcal{I})$ is called $\star$-codense if $X \setminus A$ is $\star$-dense.*

Definition 1.8 *[5] An ideal topological space $(X,\tau,\mathcal{I})$ is called $\mathcal{I}$-submaximal if every $\star$-dense subset of X is open.*

Characterizations of semi-$\mathcal{I}_\omega$-open sets

Definition 2.1 *A subset A of an ideal topological space $(X,\tau,\mathcal{I})$ is said to be*

1. semi-$\mathcal{I}_\omega$-open if $A \subset Cl^\star(Int_\omega(A))$.
2. semi-$\mathcal{I}_\omega$-closed if $Int^\star(Cl_\omega(A)) \subset A$.

The complement of a semi-$\mathcal{I}_\omega$-open set is called semi-$\mathcal{I}_\omega$-closed.

Example 2.2 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$, the subset $A = \mathbb{Q}^\star$ is semi-$\mathcal{I}_\omega$-open for $Cl^\star(Int_\omega(A)) = Cl^\star(A) = Cl(A) = \mathbb{R} \supset A$.*

Example 2.3 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$, the subset $A = \mathbb{Q}$ is not semi-$\mathcal{I}_\omega$-open for $Cl^*(Int_\omega(\mathbb{Q})) = Cl^*(\phi) = \phi \not\supseteq \mathbb{Q}$.*

Proposition 2.4 *In an ideal topological space $(X, \tau, \mathcal{I})$, every semi-$\mathcal{I}_\omega$-open subset is semi-ω-open.*

Proof. Let A be semi-$\mathcal{I}_\omega$-open in $(X, \tau, \mathcal{I})$. Then $A \subset Cl^*(Int_\omega(A)) \subset Cl(Int_\omega(A))$. This proves that A is semi-ω-open.

Remark 2.5 *The converse of Proposition 2.4 is not true.*

Example 2.6 *In $\mathbb{R}$ with the topology $\tau = \{\phi, \mathbb{R}, \mathbb{Q}\}$ and ideal $\mathcal{I} = \mathbb{P}(\mathbb{R})$, $A = \mathbb{Q} \cup \{\sqrt{2}\}$ is semi-ω-open for $Cl(Int_\omega(A)) = Cl(\mathbb{Q}) = \mathbb{R} \supset A$. But A is not semi-$\mathcal{I}_\omega$-open for $Cl^*(Int_\omega(A)) = Cl^*(\mathbb{Q}) = \mathbb{Q} \not\supseteq A$.*

Theorem 2.7 *For a subset of an ideal topological space $(X, \tau, \mathcal{I})$, the following properties hold:*

1. Every ω-open set is semi-$\mathcal{I}_\omega$-open.
2. Every open set is semi-$\mathcal{I}_\omega$-open.
3. Every α-$\mathcal{I}_\omega$-open set is semi-$\mathcal{I}_\omega$-open.
4. Every semi-$\mathcal{I}_\omega$-open set is β-$\mathcal{I}_\omega$-open.
5. Every semi-$\mathcal{I}_\omega$-open set is b-$\mathcal{I}_\omega$-open.

Proof.

(1) If A is ω-open, then $A \subset Cl^*(A) = Cl^*(Int_\omega(A))$. Therefore A is semi-$\mathcal{I}_\omega$-open.
(2) If A is open, then $A \subset Cl^*(A) = Cl^*(Int_\omega(A)) \subset Cl^*(Int_\omega(A))$. Therefore A is semi-$\mathcal{I}_\omega$-open.
(3) If A is α-$\mathcal{I}_\omega$-open, then $A \subset Int_\omega(Cl^*(Int_\omega(A))) \subset Cl^*(Int_\omega(A))$. Therefore A is semi-$\mathcal{I}_\omega$-open.
(4) If A is semi-$\mathcal{I}_\omega$-open, then $A \subset Cl^*(Int_\omega(A)) \subset Cl^*(Int_\omega(Cl^*(A)))$. Therefore A is β-$\mathcal{I}_\omega$-open.
(5) If A is semi-$\mathcal{I}_\omega$-open, then $A \subset Cl^*(Int_\omega(A)) \subset Int_\omega(Cl^*(A)) \cup Cl^*(Int_\omega(A))$. Therefore A is b-$\mathcal{I}_\omega$-open.

The following Examples support that the separate converses of Theorem 2.7 are not true in general.

Example 2.8 *In $\mathbb{R}$ with the topology $\tau = \{\phi, \mathbb{R}, \mathbb{N}, \mathbb{Q}^*, \mathbb{Q}^* \cup \mathbb{N}\}$ and ideal $\mathcal{I} = \{\phi\}$,*

1. $A = \mathbb{Q}$ is semi-$\mathcal{I}_\omega$-open, since $Cl^*(Int_\omega(A)) = Cl^*(\mathbb{N}) = Cl(\mathbb{N}) = \mathbb{Q} \supset A$. But $A = \mathbb{Q}$ is not ω-open, since $Int_\omega(A) = \mathbb{N} \neq A$.
2. $A = \mathbb{Q}$ is semi-$\mathcal{I}_\omega$-open by (1), but not open.

Example 2.9 *By (1) of Example 2.8, $A = \mathbb{Q}$ is semi-$\mathcal{I}_\omega$-open. But $Int_\omega(Cl^*(Int_\omega(A))) = Int_\omega(Cl^*(\mathbb{N})) = Int_\omega(Cl(\mathbb{N})) = Int_\omega(\mathbb{Q}) = \mathbb{N} \not\supseteq \mathbb{Q} = A$.*

Example 2.10 *In $\mathbb{R}$ with usual topology τ_u and $\mathcal{I} = \mathbb{F}$, the ideal of all finite subsets of $\mathbb{R}$,*

(1)$A = \mathbb{Q}$ is β-$\mathcal{I}_\omega$-open, since $Cl^*(Int_\omega(Cl^*(A))) = Cl^*(Int_\omega(\mathbb{R})) = Cl^*(\mathbb{R}) = \mathbb{R} \supset \mathbb{Q} = A$. But $A = \mathbb{Q}$ is not semi-$\mathcal{I}_\omega$-open, since $Cl^*(Int_\omega(A)) = Cl^*(\phi) = \phi \not\supseteq \mathbb{Q} = A$.

(2)$A = \mathbb{Q}$ is b-$\mathcal{I}_\omega$-open, since $Int_\omega(Cl^*(A)) \cup Cl^*(Int_\omega(A)) = Int_\omega(\mathbb{R}) \cup Cl^*(\phi) = \mathbb{R} \cup \phi = \mathbb{R} \supset A$. But $A = \mathbb{Q}$ is not semi-$\mathcal{I}_\omega$-open by (1).

Theorem 2.11 *Let A be a subset of an ideal topological space $(X, \tau, \mathcal{I})$. Then A is α-$\mathcal{I}_\omega$-open if and only if it is semi-$\mathcal{I}_\omega$-open and pre-$\mathcal{I}_\omega$-open.*

Proof.
Let A be an α-$\mathcal{I}_\omega$-open. Then $A \subset Int_\omega(Cl^\star(Int_\omega(A))) \subset Cl^\star(Int_\omega(A))$. Also $A \subset Int_\omega(Cl^\star(Int_\omega(A))) \subset Int_\omega(Cl^\star(A))$. Thus A is semi-$\mathcal{I}_\omega$-open and pre-$\mathcal{I}_\omega$-open.

Conversely, let A be semi-$\mathcal{I}_\omega$-open and pre-$\mathcal{I}_\omega$-open. Then $A \subset Cl^\star(Int_\omega(A))$ and $A \subset Int_\omega(Cl^\star(A))$. Hence $A \subset Int_\omega(Cl^\star(A)) \subset Int_\omega(Cl^\star(Cl^\star(Int_\omega(A)))) = Int_\omega(Cl^\star(Int_\omega(A)))$ which implies that A is α-$\mathcal{I}_\omega$-open.

Remark 2.12 *The following Examples show that the notions of semi-$\mathcal{I}_\omega$-openness and pre-$\mathcal{I}_\omega$-openness are independent.*

Example 2.13 *By (1) of Example 2.8, $A = \mathbb{Q}$ is semi-$\mathcal{I}_\omega$-open. But $A = \mathbb{Q}$ is not pre-$\mathcal{I}_\omega$-open for $Int_\omega(Cl^\star(A)) = Int_\omega(Cl(A)) = Int_\omega(A) = \mathbb{N} \not\supseteq \mathbb{Q} = A$.*

Example 2.14 *In Example 2.10, $A = \mathbb{Q}$ is pre-$\mathcal{I}_\omega$-open, since $A \subset Int_\omega(Cl^\star(A)) = Int_\omega(\mathbb{R}) = \mathbb{R} \supset \mathbb{Q} = A$. But $A = \mathbb{Q}$ is not semi-$\mathcal{I}_\omega$-open by (1) of Example 2.10.*

Proposition 2.15 *The intersection of a semi-$\mathcal{I}_\omega$-open set and an open set is semi-$\mathcal{I}_\omega$-open.*

Proof.
Let A be semi-$\mathcal{I}_\omega$-open and U be open in X. Then $A \subset Cl^\star(Int_\omega(A))$ and $Int(U) = U$. By Lemma 1.5, we have $U \cap A \subset U \cap Cl^\star(Int_\omega(A)) = U \cap ((Int_\omega(A))^\star \cup Int_\omega(A)) = (U \cap (Int_\omega(A))^\star) \cup (U \cap Int_\omega(A)) \subset (U \cap Int_\omega(A))^\star \cup (U \cap Int_\omega(A)) = Cl^\star(U \cap Int_\omega(A)) = Cl^\star(Int_\omega(U) \cap Int_\omega(A)) = Cl^\star(Int_\omega(U \cap H))$ which proves that $U \cap A$ is semi-$\mathcal{I}_\omega$-open.

Remark 2.16 *The intersection of two semi-$\mathcal{I}_\omega$-open sets need not be semi-$\mathcal{I}_\omega$-open as can be seen from the following Example.*

Example 2.17 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$, A = (0,1] is semi-$\mathcal{I}_\omega$-open for $Cl^\star(Int_\omega(A)) = Cl^\star((0,1)) = Cl((0,1)) = [0,1] \supset A$. Similarly B = [1,2) is also semi-$\mathcal{I}_\omega$-open. But $A \cap B$ = {1} is not semi-$\mathcal{I}_\omega$-open for $Cl^\star(Int_\omega(A \cap B)) = Cl^\star(Int_\omega(\{1\})) = Cl^\star(\phi) = \phi \not\supseteq \{1\} = A \cap B$.*

Theorem 2.18 *If a subset A of an ideal topological space $(X, \tau, \mathcal{I})$ is both $\star$-closed and β-$\mathcal{I}_\omega$-open, then A is semi-$\mathcal{I}_\omega$-open.*

Proof. Since A is β-$\mathcal{I}_\omega$-open, $A \subset Cl^\star(Int_\omega(Cl^\star(A))) = Cl^\star(Int_\omega(A))$, A being $\star$-closed. Therefore A is semi-$\mathcal{I}_\omega$-open.

Theorem 2.19 *If a subset A of an ideal topological space $(X, \tau, \mathcal{I})$ is both β-$\mathcal{I}_\omega$-open and a t-$\mathcal{I}_\omega$-set, then A is semi-$\mathcal{I}_\omega$-open.*

Proof. Since A is a t-$\mathcal{I}_\omega$-set, $Int(A) = Int_\omega(Cl^\star(A))$. Also A is β-$\mathcal{I}_\omega$-open implies $A \subset Cl^\star(Int_\omega(Cl^\star(A))) \subset Cl^\star(Int(A)) \subset Cl^\star(Int_\omega(A))$. Therefore A is semi-$\mathcal{I}_\omega$-open.

Theorem 2.20 *If a subset A of an ideal topological space $(X, \tau, \mathcal{I})$ is both B-$\mathcal{I}_\omega$-open and a t-$\mathcal{I}_\omega$-set, then A is semi-$\mathcal{I}_\omega$-open.*

Proof. Since A is a t-$\mathcal{I}_\omega$-set, $Int_\omega(Cl^\star(A)) = Int(A) \subset Int_\omega(A)$. Also A is b-$\mathcal{I}_\omega$-open implies $A \subset Int_\omega(Cl^\star(A)) \cup Cl^\star(Int_\omega(A)) \subset Int_\omega(A) \cup Cl^\star(Int_\omega(A)) = Cl^\star(Int_\omega(A))$. Therefore A is semi-$\mathcal{I}_\omega$-open.

Proposition 2.21 *A subset A of an ideal topological space $(X, \tau, \mathcal{I})$ is semi-$\mathcal{I}_\omega$-open if and only if $Cl^\star(A) = Cl^\star(Int_\omega(A))$.*

Proof. Let A be semi-$\mathcal{I}_\omega$-open. Then $A \subset Cl^\star(Int_\omega(A))$ and $Cl^\star(A) \subset Cl^\star(Int_\omega(A))$. But $Cl^\star(Int_\omega(A)) \subset Cl^\star(A)$. Thus $Cl^\star(A) = Cl^\star(Int_\omega(A))$.

Conversely, let the condition hold. We have $A \subset Cl^\star(A) = Cl^\star(Int_\omega(A))$, by assumption. Thus $A \subset Cl^\star(Int_\omega(A))$ and hence A is semi-$\mathcal{I}_\omega$-open.

Proposition 2.22 *In $(X, \tau, \mathcal{I})$ if A is a b-$\mathcal{I}_\omega$-open set such that $Cl^\star(A) = \phi$, then A is semi-$\mathcal{I}_\omega$-open.*

Theorem 2.23 *For a subset A of an $\mathcal{I}$-submaximal ideal space $(X, \tau, \mathcal{I})$, the following are equivalent.*

(1)A is semi-$\mathcal{I}_\omega$-open,

(2)A is β-$\mathcal{I}_\omega$-open.

Proof. (1)⇒(2): from (4) of Theorem 2.7.

(2)⇒(1): Let A be a β-$\mathcal{I}_\omega$-open set in X. Then $A \subset Cl^\star(Int_\omega(Cl^\star(A)))$ and $Cl^\star(A) \subset Cl^\star(Int_\omega(Cl^\star(A)))$. Thus, $Cl^\star(A)$ is semi-$\mathcal{I}_\omega$-open. Put $A = Cl^\star(A)$ and $K = A \cup (X \backslash Cl^\star(A))$. We have $A = Cl^\star(A) \cap K$ and $Cl^\star(K) = X$. This implies that $A = A \cap K$, where A is semi-$\mathcal{I}_\omega$-open and K is $\star$-dense. Since X is $\mathcal{I}$-submaximal, K is open. By Proposition 2.15, $A = A \cap K$ is semi-$\mathcal{I}_\omega$-open.

Theorem 2.24 *A subset A of an ideal topological space $(X, \tau, \mathcal{I})$ is semi-$\mathcal{I}_\omega$-open if and only if there exists $U \in \tau_\omega$ such that $U \subset A \subset Cl^\star(U)$.*

Proof. Let A be semi-$\mathcal{I}_\omega$-open. Then $A \subset Cl^\star(Int_\omega(A))$. Take $Int_\omega(A) = U$. Then $U \subset A \subset Cl^\star(U)$.

Conversely, let $U \subset A \subset Cl^\star(U)$ for some $U \in \tau_\omega$. Since $U \subset A$, $U \subset Int_\omega(A)$ and $A \subset Cl^\star(U) \subset Cl^\star(Int_\omega(A))$ which implies A is semi-$\mathcal{I}_\omega$-open.

Proposition 2.25 *If A is a semi-$\mathcal{I}_\omega$-open set in an ideal topological space $(X, \tau, \mathcal{I})$ and $A \subset B \subset Cl^\star(A)$, then B is semi-$\mathcal{I}_\omega$-open.* By assumption $B \subset Cl^\star(A) \subset Cl^\star(Cl^\star(Int_\omega(A)))$ (for A is semi-$\mathcal{I}_\omega$-open) = $Cl^\star(Int_\omega(A)) \subset Cl^\star(Int_\omega(B))$ by assumption. This implies B is semi-$\mathcal{I}_\omega$-open.

Characterizations of δ-$\mathcal{I}_\omega$-open sets

Definition 3.1 *A subset A of an ideal topological space $(X, \tau, \mathcal{I})$ is said to be*

1. δ-$\mathcal{I}_\omega$-open if $Int_\omega(Cl^\star(A)) \subset Cl^\star(Int_\omega(A))$.
2. δ-$\mathcal{I}_\omega$-closed if $Int^\star(Cl_\omega(A)) \subset Cl_\omega(Int^\star(A))$.

The complement of a δ-$\mathcal{I}_\omega$-open set is called δ-$\mathcal{I}_\omega$-closed.

Example 3.2 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$, for the subset $\mathbb{Q}$, $Int_\omega(Cl^\star(\mathbb{Q})) = Int_\omega(Cl(\mathbb{Q})) = Int_\omega(\mathbb{R}) = \mathbb{R}$ and $Cl^\star(Int_\omega(\mathbb{Q})) = Cl^\star(\phi) = \phi$. Thus $Int_\omega(Cl^\star(\mathbb{Q})) \nsubseteq Cl^\star(Int_\omega(\mathbb{Q}))$ which proves that $\mathbb{Q}$ is not δ-$\mathcal{I}_\omega$-open.*

Example 3.3 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$, for the subset $A = \{1\}$, $Int_\omega(Cl^\star(A)) = Int_\omega(Cl(A)) = Int_\omega(A) = \phi$ and $Cl^\star(Int_\omega(A)) = Cl^\star(\phi) = \phi$. Thus $Int_\omega(Cl^\star(A)) \subset Cl^\star(Int_\omega(A))$ which proves that A is δ-$\mathcal{I}_\omega$-open.*

Proposition 3.4 *For a subset A of an ideal topological space $(X, \tau, \mathcal{I})$, the following properties hold:*

(1) Every α-$\mathcal{I}_\omega$-open set is δ-$\mathcal{I}_\omega$-open.

(2) Every t-$\mathcal{I}_\omega$-set is δ-$\mathcal{I}_\omega$-open.

Proof.(1) Since A is α-$\mathcal{I}_\omega$-open, $A \subset Int_\omega(Cl^\star(Int_\omega(A))) \subset Cl^\star(Int_\omega(A))$. So $Cl^\star(A) \subset Cl^\star(Int_\omega(A))$ and $Int_\omega(Cl^\star(A)) \subset Cl^\star(A) \subset Cl^\star(Int_\omega(A))$. Therefore A is δ-$\mathcal{I}_\omega$-open.

(2) Since A is an t-$\mathcal{I}_\omega$-set, $Int_\omega(Cl^\star(A)) = Int(A) \subset A$. Then $Int_\omega(Cl^\star(A)) \subset Int_\omega(A) \subset Cl^\star(Int_\omega(A))$. Therefore A is δ-$\mathcal{I}_\omega$-open.

The converses of (1) and (2) in Proposition 3.4 are not true in general as seen from the following Example.

Example 3.5 (1) In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$, the subset $A = \{1\}$ is δ-$\mathcal{I}_\omega$-open by Example 3.3. But A is not α-$\mathcal{I}_\omega$-open for $Int_\omega(Cl^\star(Int_\omega(A))) = Int_\omega(Cl^\star(Int_\omega(A))) = Int_\omega(Cl^\star(\phi)) = Int_\omega(\phi) = \phi \supsetneq \{1\} = A$.

(2) In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$, for the subset $A = \mathbb{Q}^*$, $Int_\omega(Cl^*(A)) = Int_\omega(Cl(A)) = Int_\omega(\mathbb{R}) = \mathbb{R}$ and $Cl^*(Int_\omega(A)) = Cl^*(A) = Cl(A) = \mathbb{R}$. Thus $Int_\omega(Cl^*(A)) \subset Cl^*(Int_\omega(A))$ and hence A is δ-$\mathcal{I}_\omega$-open. But H is not a t-$\mathcal{I}_\omega$-set for $Int_\omega(Cl^*(A)) = Int_\omega(Cl(A)) = Int_\omega(\mathbb{R}) = \mathbb{R} \neq \phi = Int(A)$.

Definition 3.6 *A subset A of an ideal topological space $(X, \tau, \mathcal{I})$ is said to be β-$\mathcal{I}_\omega$-closed if $Int^*(Cl_\omega(Int^*(A))) \subset A$.*

The complement of a β-$\mathcal{I}_\omega$-open set is called β-$\mathcal{I}_\omega$-closed.

Proposition 3.7 *A subset A of an ideal topological space $(X, \tau, \mathcal{I})$ is β-$\mathcal{I}_\omega$-closed if and only if $Int^*(Cl_\omega(Int^*(A))) = Int^*(A)$.*

Proof. Since A is β-$\mathcal{I}_\omega$-closed set, $Int^*(Cl_\omega(Int^*(A))) \subset A$ and hence $Int^*(Cl_\omega(Int^*(A))) \subset Int^*(A)$. Also $Int^*(A) \subset Cl_\omega(Int^*(A))$ and hence $Int^*(A) \subset Int^*(Cl_\omega(Int^*(A)))$. Thus $Int^*(Cl_\omega(Int^*(A))) = Int^*(A)$.

Conversely, let the condition hold. We have $Int^*(Cl_\omega(Int^*(A))) = Int^*(A) \subset A$. Therefore A is β-$\mathcal{I}_\omega$-closed.

Theorem 3.8 *For a subset A of an ideal topological space $(X, \tau, \mathcal{I})$, the following properties are equivalent.*

1. A is semi-$\mathcal{I}_\omega$-closed.
2. A is β-$\mathcal{I}_\omega$-closed and δ-$\mathcal{I}_\omega$-closed.

Proof.(1)⇒(2): Let A be semi-$\mathcal{I}_\omega$-closed. By (4) of Theorem 2.7, A is β-$\mathcal{I}_\omega$-closed. Since A is semi-$\mathcal{I}_\omega$-closed, $Int^*(Cl_\omega(A)) \subset A$ and so $Int^*(Cl_\omega(A)) \subset Int^*(A)$ which implies $Cl_\omega(Int^*(Cl_\omega(A))) \subset Cl_\omega(Int^*(A))$. Thus $Int^*(Cl_\omega(A)) \subset Cl_\omega(Int^*(Cl_\omega(A))) \subset Cl_\omega(Int^*(A))$ and so A is δ-$\mathcal{I}_\omega$-closed.

(2)⇒(1): Since A is δ-$\mathcal{I}_\omega$-closed, $Int^*(Cl_\omega(A)) \subset Cl_\omega(Int^*(A))$ and so $Int^*(Cl_\omega(A)) \subset Int^*(Cl_\omega(Int^*(A))) \subset A$ since A is β-$\mathcal{I}_\omega$-closed. Thus A is semi-$\mathcal{I}_\omega$-closed.

Remark 3.9 *The following Examples show that the concepts of β-$\mathcal{I}_\omega$-closedness and δ-$\mathcal{I}_\omega$-closedness are independent.*

Example 3.10 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$, the subset $A = \mathbb{R} - \{1\}$ is δ-$\mathcal{I}_\omega$-closed by Example 3.3. But $Int^*(Cl_\omega(Int^*(A))) = Int^*(Cl_\omega(Int(A))) = Int^*(Cl_\omega(A)) = Int^*(\mathbb{R}) = Int(\mathbb{R}) = \mathbb{R} \not\subseteq \mathbb{R} - \{1\} = A$ which proves that A is not β-$\mathcal{I}_\omega$-closed.*

Example 3.11 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$, the subset $A = \mathbb{Q}^*$ is not δ-$\mathcal{I}_\omega$-closed for $\mathbb{Q}$ is not δ-$\mathcal{I}_\omega$-open by Example 3.2. But $Int^*(Cl_\omega(Int^*(A))) = Int^*(Cl_\omega(Int(A))) = Int^*(Cl_\omega(\phi)) = Int^*(\phi) = \phi \subset A$. Thus $A = \mathbb{Q}^*$ is β-$\mathcal{I}_\omega$-closed.*

Theorem 3.12 *Let $(X, \tau, \mathcal{I})$ be an ideal topological space. Then a subset of X is α-$\mathcal{I}_\omega$-open if and only if it is both δ-$\mathcal{I}_\omega$-open and pre-$\mathcal{I}_\omega$-open.*

*Proof.*Necessity: Let A be an α-$\mathcal{I}_\omega$-open set. Then $A \subset Int_\omega(Cl^*(Int_\omega(A)))$. It implies that $Cl^*(A) \subset Cl^*(Int_\omega(A))$ and $Int_\omega(Cl^*(A)) \subset Int_\omega(Cl^*(Int_\omega(A))) \subset Cl^*(Int_\omega(A))$. Hence, A is a δ-$\mathcal{I}_\omega$-open set. On the other hand, since A is an α-$\mathcal{I}_\omega$-open set, A is a pre-$\mathcal{I}_\omega$-open set by Theorem 2.11.

Sufficiency: Let A be both δ-$\mathcal{I}_\omega$-open and pre-$\mathcal{I}_\omega$-open. Since A is δ-$\mathcal{I}_\omega$-open, $Int_\omega(Cl^*(A)) \subset Cl^*(Int_\omega(A))$ and hence $Int_\omega(Cl^*(A)) \subset Int_\omega(Cl^*(Int_\omega(A)))$. Since A is pre-$\mathcal{I}_\omega$-open, $A \subset Int_\omega(Cl^*(A)) \subset Int_\omega(Cl^*(Int_\omega(A)))$ which proves that A is an α-$\mathcal{I}_\omega$-open set.

Remark 3.13 *The following Examples show that the notions of δ-$\mathcal{I}_\omega$-openness and pre-$\mathcal{I}_\omega$-openness are independent.*

Example 3.14 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \mathbb{P}(\mathbb{R})$, $A = (0,1]$ is δ-$\mathcal{I}_\omega$-open, since $Int_\omega(Cl^*(A)) = Int_\omega(A) = (0,1)$ and $Cl^*(Int_\omega(A)) = Cl^*((0,1)) = (0,1)$. But $A = (0,1]$ is not pre-$\mathcal{I}_\omega$-open, since $Int_\omega(Cl^*(A)) = Int_\omega(A) = (0,1) \not\supseteq A$.*

Example 3.15 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$, $A = \mathbb{Q}$ is pre-$\mathcal{I}_\omega$-open, since $Int_\omega(Cl^*(A)) = Int_\omega(Cl(A)) = Int_\omega(\mathbb{R}) = \mathbb{R} \supset \mathbb{Q} = A$. But $Cl^*(Int_\omega(A)) = Cl^*(\phi) = \phi$ and $Int_\omega(Cl^*(A)) = \mathbb{R}$ implies $Int_\omega(Cl^*(A)) \not\subseteq Cl^*(Int_\omega(A))$. Thus A is not δ-$\mathcal{I}_\omega$-open.*

Proposition 3.16 *Let A and B be subsets of an ideal topological space $(X, \tau, \mathcal{I})$. If $A \subset B \subset Cl^*(A)$ and A is δ-$\mathcal{I}_\omega$-open in X, then B is δ-$\mathcal{I}_\omega$-open in X.*

Proof. Suppose that $A \subset B \subset Cl^*(A)$ and A is δ-$\mathcal{I}_\omega$-open in X. Then $Int_\omega(Cl^*(A)) \subset Cl^*(Int_\omega(A)) \subset Cl^*(Int_\omega(B))$. Since $B \subset Cl^*(A)$, $Cl^*(B) \subset Cl^*(Cl^*(A)) = Cl^*(A)$ and $Int_\omega(Cl^*(B)) \subset Int_\omega(Cl^*(A))$. Therefore $Int_\omega(Cl^*(B)) \subset Cl^*(Int_\omega(B))$. This shows that B is a δ-$\mathcal{I}_\omega$-open set.

Corollary 3.17 *Let $(X, \tau, \mathcal{I})$ be an ideal topological space. If $A \subset X$ is δ-$\mathcal{I}_\omega$-open and $\star$-dense in $(X, \tau, \mathcal{I})$, then every subset of X containing A is δ-$\mathcal{I}_\omega$-open.*

It is obvious by Proposition 3.16.

Characterizations of semi *-$\mathcal{I}_\omega$-open sets

Definition 4.1 *A subset A of an ideal topological space $(X, \tau, \mathcal{I})$ is said to be*

1. semi *-$\mathcal{I}_\omega$-open if $A \subset Cl_\omega(Int^*(A))$.
2. semi *-$\mathcal{I}_\omega$-closed if $Int_\omega(Cl^*(A)) \subset A$.

The complement of a semi *-$\mathcal{I}_\omega$-open set is called semi *-$\mathcal{I}_\omega$-closed.

Example 4.2 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$, $A = \mathbb{R}\backslash\{0\}$ is not semi *-$\mathcal{I}_\omega$-closed, since $Int_\omega(Cl^*(A)) = Int_\omega(Cl(A)) = Int_\omega(\mathbb{R}) = \mathbb{R} \not\subseteq A$.*

Example 4.3 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \mathbb{P}(\mathbb{R})$, $A = \mathbb{R}\backslash\{0\}$ is semi *-$\mathcal{I}_\omega$-closed, since $Int_\omega(Cl^*(A)) = Int_\omega(A) = A \subset A$.*

Proposition 4.4 *For a subset of an ideal topological space $(X, \tau, \mathcal{I})$, every semi *-ω-open set is semi *-$\mathcal{I}_\omega$-open.*

Proof. If A is semi *-ω-open, then $A \subset Cl_\omega(Int(A)) \subset Cl_\omega(Int^*(A))$. Therefore A is semi *-$\mathcal{I}_\omega$-open.

Remark 4.5 *The converse of Proposition 4.4 is not true.*

Example 4.6 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \mathbb{P}(\mathbb{R})$, $A = \mathbb{Q}$ is semi *-$\mathcal{I}_\omega$-closed, since $Int_\omega(Cl^*(A)) = Int_\omega(A) = \phi \subset A$. But $A = \mathbb{Q}$ is not semi *-ω-closed, since $Int_\omega(Cl(A)) = Int_\omega(\mathbb{R}) = \mathbb{R} \not\subseteq A$.*

Proposition 4.7 *A subset A of an ideal topological space $(X, \tau, \mathcal{I})$ is semi *-$\mathcal{I}_\omega$-open if and only if $Cl_\omega(A) = Cl_\omega(Int^*(A))$.*

Proof. If A is semi *-$\mathcal{I}_\omega$-open set, then $A \subset Cl_\omega(Int^*(A))$ and $Cl_\omega(A) \subset Cl_\omega(Int^*(A))$. But $Cl_\omega(Int^*(A)) \subset Cl_\omega(A)$. Hence $Cl_\omega(A) = Cl_\omega(Int^*(A))$.

Conversely, $A \subset Cl_\omega(A) = Cl_\omega(Int^*(A))$ by assumption. Therefore A is semi *-$\mathcal{I}_\omega$-open.

Definition 4.8 *A subset A of an ideal topological space $(,,\mathcal{I})$ is said to be a t-$\mathcal{I}_\star$-set if $(^*()) = ()$.*

Example 4.9 *In $\mathbb{R}$ with usual topology and ideal $\mathcal{I} = \{\}$,*

1. $= (0,1]$ is a t-$\mathcal{I}_\star$-set, since $() = (0,1)$ and $(^*()) = (()) = ([0,1]) = (0,1)$.
2. $= \mathbb{Q}^*$ is not a t-$\mathcal{I}_\star$-set, since $() =$ and $(^*()) = (()) = (\mathbb{R}) = \mathbb{R}$.

Proposition 4.10 *In an ideal topological space* $(, , \mathcal{I})$*, every* $\star$*-closed set is a t-*$\mathcal{I}^{\star}$*-set.*

Proof. Let be a $\star$-closed set. Then $= {}^{*}()$ and $({}^{*}()) = ()$ which proves that is a t-$\mathcal{I}^{\star}$-set.

Remark 4.11 *The converse of Proposition 4.10 is not true.*

Example 4.12 *In* $\mathbb{R}$ *with usual topology and ideal* $\mathcal{I} = \{\}$, $= (0,1]$ *is t-*$\mathcal{I}^{\star}$*-set by (1) of Example 4.9. But* $= (0,1]$ *is not* $\star$*-closed, since* ${}^{*}() = () = [0,1] \neq$.

Proposition 4.13 *In an ideal topological space* $(, , \mathcal{I})$*, every t-*$\mathcal{I}$*-set is t-*$\mathcal{I}^{\star}$*-set.*

Proof. If is a t-$\mathcal{I}$-set, then $({}^{*}()) = () \subset () \subset ({}^{*}())$. Thus $({}^{*}()) = ()$ and hence is a t-$\mathcal{I}^{\star}$-set.

Remark 4.14 *The converse of Proposition 4.13 is not true.*

Example 4.15 *In* $\mathbb{R}$ *with usual topology* τ_u *and ideal* $\mathcal{I} = \mathbb{P}(\mathbb{R})$, $A = (0,1) \cap \mathbb{Q}^{*}$ *is a t-*$\mathcal{I}_{\omega}^{\star}$*-set since* $Int_{\omega}(Cl^{*}(A)) = Int_{\omega}(A)$*. But A is not a t-*$\mathcal{I}_{\omega}$*-set since* $Int_{\omega}(Cl^{*}(A)) = Int_{\omega}(A) = A \neq \phi = int(A)$.

Theorem 4.16 *A subset* A *of an ideal topological space* $(X, \tau, \mathcal{I})$ *is semi* **-*$\mathcal{I}_{\omega}$*-closed if and only if* A *is a t-*$\mathcal{I}_{\omega}^{\star}$*-set.*

Proof. A is a semi *-$\mathcal{I}_{\omega}$-closed in $X \Leftrightarrow X \backslash A$ is semi *-$\mathcal{I}_{\omega}$-open $\Leftrightarrow Cl_{\omega}(X \backslash A) = Cl_{\omega}(Int^{*}(X \backslash A))$ by Proposition 4.7 $\Leftrightarrow X \backslash Int_{\omega}(A) = X \backslash Int_{\omega}(Cl^{*}(A)) \Leftrightarrow Int_{\omega}(A) = Int_{\omega}(Cl^{*}(A)) \Leftrightarrow$ A is a t-$\mathcal{I}_{\omega}^{\star}$-set.

Proposition 4.17 *If* A *and* B *are t-*$\mathcal{I}_{\omega}^{\star}$*-sets of an ideal topological space* $(X, \tau, \mathcal{I})$*, then* $A \cap B$ *is a t-*$\mathcal{I}_{\omega}^{\star}$*-set.*

Proof. Let A and B be t-$\mathcal{I}_{\omega}^{\star}$-sets. Then $Int_{\omega}(A \cap B) \subset Int_{\omega}(Cl^{*}(A \cap B)) \subset Int_{\omega}(Cl^{*}(A) \cap Cl^{*}(B)) = Int_{\omega}(Cl^{*}(A)) \cap Int_{\omega}(Cl^{*}(B)) = Int_{\omega}(A) \cap Int_{\omega}(B) = Int_{\omega}(A \cap B)$. Thus $Int_{\omega}(A \cap B) = Int_{\omega}(Cl^{*}(A \cap B))$ and hence $A \cap B$ is a t-$\mathcal{I}_{\omega}^{\star}$-set.

Definition 4.18 *A subset* A *of an ideal topological space* $(X, \tau, \mathcal{I})$ *is said to be semi-*$\mathcal{I}_{\omega}$*-regular if* A *is semi-*$\mathcal{I}_{\omega}$*-open and a t-*$\mathcal{I}_{\omega}^{\star}$*-set.*

Example 4.19 *In* $\mathbb{R}$ *with usual topology* τ_u *and ideal* $\mathcal{I} = \{\phi\}$,

1. $A = (0,1]$ is a t-$\mathcal{I}_{\omega}^{\star}$-set by (1) of Example 4.9. Also $Cl^{*}(Int_{\omega}(A)) = Cl^{*}((0,1)) = Cl((0,1)) = [0,1] \supset A$. Thus A is semi-$\mathcal{I}_{\omega}$-open. Hence (0, 1] is semi-$\mathcal{I}_{\omega}$-regular.

2. $A = \mathbb{Q}^{*}$ is not a t-$\mathcal{I}_{\omega}^{\star}$-set by (2) of Example 4.9. Hence $\mathbb{Q}^{*}$ is not semi-$\mathcal{I}_{\omega}$-regular.

Remark 4.20 *In an ideal topological space* $(X, \tau, \mathcal{I})$,

1. Every semi-$\mathcal{I}_{\omega}$-regular set is semi-$\mathcal{I}_{\omega}$-open.

2. Every semi-$\mathcal{I}_{\omega}$-regular set is t-$\mathcal{I}_{\omega}^{\star}$-set.

The converses of (1) and (2) in Remark 4.20 are not true in general as illustrated in the following Examples.

Example 4.21 *In* $\mathbb{R}$ *with usual topology* τ_u *and ideal* $\mathcal{I} = \{\phi\}$*, the subset* $A = \mathbb{Q}^{*}$ *is semi-*$\mathcal{I}_{\omega}$*-open by Example 2.2. But* $A = \mathbb{Q}^{*}$ *is not semi-*$\mathcal{I}_{\omega}$*-regular by (2) of Example 4.19.*

Example 4.22 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$, $\mathbb{N}$ = the set of all natural numbers is a t-$\mathcal{I}_{\omega^*}$-set for $Int_\omega(Cl^*(\mathbb{N})) = Int_\omega(Cl(\mathbb{N})) = Int_\omega(\mathbb{N})$. But $\mathbb{N}$ is not semi-$\mathcal{I}_\omega$-regular for $\mathbb{N}$ is not semi-$\mathcal{I}_\omega$-open since $Cl^*(Int_\omega(\mathbb{N})) = Cl^*(\phi) = \phi \not\supseteq \mathbb{N}$.*

Theorem 4.23 *A subset of an ideal topological space $(X, \tau, \mathcal{I})$ is semi-$\mathcal{I}_\omega$-regular if and only if it is both β-$\mathcal{I}_\omega$-open and semi *-$\mathcal{I}_\omega$-closed.*

Proof. If A is semi-$\mathcal{I}_\omega$-regular, then A is both semi-$\mathcal{I}_\omega$-open and a t-$\mathcal{I}_{\omega^*}$-set. Since A is semi-$\mathcal{I}_\omega$-open, A is β-$\mathcal{I}_\omega$-open by (4) of Theorem 2.7. Also A is a t-$\mathcal{I}_{\omega^*}$-set by assumption. Hence A is semi *-$\mathcal{I}_\omega$-closed.

Conversely, let A be semi *-$\mathcal{I}_\omega$-closed and β-$\mathcal{I}_\omega$-open. Since A is semi *-$\mathcal{I}_\omega$-closed, by Theorem 4.16, A is a t-$\mathcal{I}_{\omega^*}$-set. Since A is β-$\mathcal{I}_\omega$-open, $A \subset Cl^*(Int_\omega(Cl^*(A))) = Cl^*(Int_\omega(A))$. Therefore A is semi-$\mathcal{I}_\omega$-open. Since A is both semi-$\mathcal{I}_\omega$-open and a t-$\mathcal{I}_{\omega^*}$-set, A is semi-$\mathcal{I}_\omega$-regular.

Remark 4.24 *The following Example shows that the notions of β-$\mathcal{I}_\omega$-openness and semi *-$\mathcal{I}_\omega$-closedness are independent.*

Example 4.25 (1) In $\mathbb{R}$ with the topology $\tau = \{\phi, \mathbb{R}, \mathbb{Q}^*\}$ and ideal $\mathcal{I} = \mathbb{P}(\mathbb{R})$, $A = \mathbb{Q}$ is semi *-$\mathcal{I}_\omega$-closed, since $Int_\omega(Cl^*(A)) = Int_\omega(A) = \phi \subset A$. But $A = \mathbb{Q}$ is not β-$\mathcal{I}_\omega$-open, since $Cl^*(Int_\omega(Cl^*(A))) = Cl^*(Int_\omega(A)) = Cl^*(\phi) = \phi \not\supseteq A$.

(2) In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$, $A = \mathbb{Q}$ is β-$\mathcal{I}_\omega$-open, since $Cl^*(Int_\omega(Cl^*(A))) = Cl^*(Int_\omega(Cl(A))) = Cl^*(Int_\omega(\mathbb{R})) = \mathbb{R} \supset A$. But $A = \mathbb{Q}$ is not semi *-$\mathcal{I}_\omega$-closed, since $Int_\omega(Cl^*(A)) = Int_\omega(Cl(A)) = Int_\omega(\mathbb{R}) = \mathbb{R} \not\subseteq A$.

Characterizations of $\mathcal{I}_\omega$-$\mathcal{R}$-closed sets

Definition 5.1 *A subset A of an ideal topological space $(X, \tau, \mathcal{I})$ is called $\mathcal{I}_\omega$-$\mathcal{R}$-closed if $A = Cl^*(Int_\omega(A))$.*

Example 5.2 *In $\mathbb{R}$ with the topology $\tau = \{\phi, \mathbb{R}, \mathbb{Q}^*\}$ and ideal $\mathcal{I} = \mathbb{P}(\mathbb{R})$,*

1. $A = \mathbb{Q}$ is not $\mathcal{I}_\omega$-$\mathcal{R}$-closed, since $Cl^*(Int_\omega(A)) = Cl^*(\phi) = \phi \neq A$.
2. $A = \mathbb{Q}^*$ is $\mathcal{I}_\omega$-$\mathcal{R}$-closed for $Cl^*(Int_\omega(A)) = Cl^*(A) = A$.

Theorem 5.3 *For a subset A of an ideal topological space $(X, \tau, \mathcal{I})$, the following properties are equivalent.*

1. $A(\neq \phi)$ is $\mathcal{I}_\omega$-$\mathcal{R}$-closed.
2. There exists a non-empty ω-open set G such that $G \subset A = Cl^*(G)$.
3. There exists a non-empty ω-open set G such that $A = G \cup (Cl^*(G) - G)$.

Proof. (1)⇒(2): Suppose $A(\neq \phi)$ is an $\mathcal{I}_\omega$-$\mathcal{R}$-closed set. Then $A = Cl^*(Int_\omega(A))$. Let $G = Int_\omega(A)$. G is the required ω-open set such that $G \subset A = Cl^*(G)$.

(2)⇒(3): Since $A = Cl^*(G) = G \cup (Cl^*(G) - G)$ where G is a nonempty ω-open set, (3) follows.

(3)⇒(1): $A = G \cup (Cl^*(G) - G)$ implies that $A = Cl^*(G) = Cl^*(Int_\omega(G)) \subset Cl^*(Int_\omega(A))$, since G is ω-open and $G \subset A$. Also $Cl^*(Int_\omega(A)) \subset Cl^*(A) = Cl^*(G) = A$. Therefore $A = Cl^*(Int_\omega(A))$ which implies that A is $\mathcal{I}_\omega$-$\mathcal{R}$-closed.

Theorem 5.4 *For each β-$\mathcal{I}_\omega$-open subset A of an ideal topological space $(X, \tau, \mathcal{I})$, $Cl^*(A)$ is $\mathcal{I}_\omega$-$\mathcal{R}$-closed.*

Proof. Suppose A is β-$\mathcal{I}_\omega$-open. Then $A \subset Cl^*(Int_\omega(Cl^*(A)))$ and so $Cl^*(A) \subset Cl^*(Int_\omega(Cl^*(A))) \subset Cl^*(A)$ which implies that $Cl^*(A) = Cl^*(Int_\omega(Cl^*(A)))$. Therefore $Cl^*(A)$ is $\mathcal{I}_\omega$-$\mathcal{R}$-closed.

Theorem 5.5 *For a subset A of an ideal topological space $(X, \tau, \mathcal{I})$, the following properties are equivalent.*

1. A is $\mathcal{I}_\omega$-$\mathcal{R}$-closed.
2. A is semi-$\mathcal{I}_\omega$-open and $\star$-closed.
3. A is β-$\mathcal{I}_\omega$-open and $\star$-closed.

Proof.(1)⇒(2): If A is $\mathcal{I}_\omega$-$\mathcal{R}$-closed, then $A = Cl^\star(Int_\omega(A))$. Since $A \subset Cl^\star(Int_\omega(A))$, A is semi-$\mathcal{I}_\omega$-open. Also, $A = Cl^\star(A)$ and thus A is $\star$-closed.

(2)⇒(3): It follows from the fact that every semi-$\mathcal{I}_\omega$-open set is a β-$\mathcal{I}_\omega$-open.

(3)⇒(1): Suppose A is β-$\mathcal{I}_\omega$-open and $\star$-closed. Then $A \subset Cl^\star(Int_\omega(Cl^\star(A)))$ and $A = Cl^\star(A)$. Now $Cl^\star(Int_\omega(A)) \subset Cl^\star(A) = A$. Also, $A \subset Cl^\star(Int_\omega(A))$. Therefore $A = Cl^\star(Int_\omega(A))$ which implies that A is $\mathcal{I}_\omega$-$\mathcal{R}$-closed.

Remark 5.6 *The following Examples show that*

1. the notions of semi-$\mathcal{I}_\omega$-openness and $\star$-closedness are independent.
2. the notions of β-$\mathcal{I}_\omega$-openness and $\star$-closedness are independent.

Example 5.7 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$,*

1. $A = \mathbb{Q}^\star$ is semi-$\mathcal{I}_\omega$-open by Example 4.21. But A is not $\star$-closed for $Cl^\star(A) = Cl(A) = \mathbb{R} \neq A$.
2. $\mathbb{N}$ = the set of natural numbers is not semi-$\mathcal{I}_\omega$-open by Example 4.22. But $\mathbb{N}$ is $\star$-closed for $Cl^\star(\mathbb{N}) = Cl(\mathbb{N}) = \mathbb{N}$.

Example 5.8 *In $\mathbb{R}$ with usual topology τ_u and ideal $\mathcal{I} = \{\phi\}$,*

1. the subset $A = \mathbb{Q}^\star$ is semi-$\mathcal{I}_\omega$-open by Example 4.21 and hence β-$\mathcal{I}_\omega$-open by (4) of Theorem 2.7. But $A = \mathbb{Q}^\star$ is not $\star$-closed for $Cl^\star(A) = Cl(A) = \mathbb{R} \neq A$.
2. $\mathbb{N}$ = the set of all natural numbers is $\star$-closed by (2) of Example 5.7. But $\mathbb{N}$ is not β-$\mathcal{I}_\omega$-open for $Cl^\star(Int_\omega(Cl^\star(\mathbb{N}))) = Cl^\star(Int_\omega(Cl(\mathbb{N}))) = Cl^\star(Int_\omega(\mathbb{N})) = Cl^\star(\phi) = \phi \not\supseteq \mathbb{N}$.

Further Characterizations

Definition 6.1 *An ideal topological space $(X, \tau, \mathcal{I})$ is called $\mathcal{I}_\omega$-sub- maximal if every $\star$-dense subset of X is ω-open.*

Proposition 6.2

(1) Every submaximal space is $\mathcal{I}$-submaximal.

(2) Every $\mathcal{I}$-submaximal space is $\mathcal{I}_\omega$-submaximal.

Proof.(1) If (X, τ) is submaximal and A is $\star$-dense in the ideal topological space $(X, \tau, \mathcal{I})$, then $Cl^\star(A) = X$. But $X = Cl^\star(A) \subset Cl(A)$ implies $Cl(A) = X$. Thus A is dense in X and by assumption A is open in X. This shows that $(X, \tau, \mathcal{I})$ is $\mathcal{I}$-submaximal.

(2) Proof follows directly since any open set is ω-open.

The converses of (1) and (2) in Proposition 6.2 are not true in general as illustrated below.

Example 6.3 (1) In $(\mathbb{R}, \tau, \mathcal{I})$ where $\tau = \tau_u$, the usual topology and ideal $\mathcal{I} = \mathbb{P}(\mathbb{R})$, if A is any $\star$-dense subset, then $Cl^\star(A) = \mathbb{R}$ and so $A = \mathbb{R}$ which is open. Thus $(\mathbb{R}, \tau_u, \mathcal{I})$ is $\mathcal{I}$-submaximal. But in $(\mathbb{R}, \tau_u)$, $\mathbb{Q}$ is dense in $\mathbb{R}$ since $Cl(\mathbb{Q}) = \mathbb{R}$. But $\mathbb{Q}$ is not open. This shows that $(\mathbb{R}, \tau_u)$ is not submaximal.

(2) In the ideal topological space $(\mathbb{N}, \tau, \mathcal{I})$, where $\mathbb{N}$ is the set of all natural numbers, $\tau = \{\phi, \mathbb{N}\}$ and ideal $\mathcal{I} = \{\phi\}$, if A is any $\star$-dense subset in $\mathbb{N}$, then $A \subset \mathbb{N}$. Since $\mathbb{N}$ is countable, A is ω-open. Thus $(\mathbb{N}, \tau, \mathcal{I})$ is $\mathcal{I}_\omega$-submaximal. The subset $A = \{1\}$ is $\star$-dense in $\mathbb{N}$ for $Cl^\star(A) = Cl(A) = \mathbb{N}$. But $A = \{1\}$ is not open in $\mathbb{N}$. This shows that $(\mathbb{N}, \tau, \mathcal{I})$ is not $\mathcal{I}$-submaximal.

Theorem 6.4 *For an ideal topological space* $(X, \tau, \mathcal{I})$*, the following are equivalent.*

1. X is $\mathcal{I}_\omega$-submaximal,
2. Every $\star$-codense subset of X is ω-closed.

*Proof.*X is $\mathcal{I}_\omega$-submaximal ⇔ every $\star$-dense subset of X is ω-open ⇔ every $\star$-co-dense subset of X is ω-closed since a subset A is $\star$-dense in X if and only if $X - A$ is $\star$-codense in X.

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RESEARCH ARTICLE

Predicting Length of Stay of Patients using Data Engineering and Ensemble based Models

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ABSTRACT

Length of Stay (LoS) in hospitals and medical costs are directly proportional. Accurately predicting the length of stay component can not only be cost effective for patients, but also be resource effective for hospitals. Hospitals can pre-determine and allocate resources according to emergency requirements. This work presents an effective Data Engineering and Ensemble based LoS (DEEL) prediction model for accurate prediction of LoS component. The model is composed of a highly operational data engineering phase, which derives highly related features for the prediction component. The model building phase creates a boosted ensemble model that enables qualitative predictions. Experiments were performed using the MIMIC III dataset, and results obtained exhibits high prediction levels with 90% accuracy levels. Comparison with existing models also indicate that the proposed model exhibits 8% increase in accuracy levels indicating the high performing nature of the model.

Keywords: Length of Stay in ICU; Data Engineering; Ensemble Modelling; Boosting; Decision Tree; MIMIC.

INTRODUCTION

Healthcare industry faces constant pressure, requiring the need to reduce healthcare costs. Sustainable hospital operations have become priority due to the increasing requirements of hospital facilities. Hospitals are also required to utilize resources effectively to maximize their revenues [1]. ICU beds form the major components of this requirement cycle, and it becomes mandatory to effectively allocate them, as human life is usually on the line.

Predicting Length of Stay (LoS) is one such technique that aids in effective prediction of the resource requirements and helps to plan for the future requirements [2]. Benefits of such prediction models are not constrained to the profitability of hospitals, they are also extended to the employees, the community and mainly the patients [3]. As cost incurred is directly proportional to the stay length in ICU, accurate predictions usually aid patients economically by initially intimating the requirements. Prior identification of length of stay of patients can even predict extended stay estimations. The benefits obtained due to effective LoS predictions, are not solely economic. They also extend to the psychological wellbeing of the patient and their caretakers/ relatives by providing a view of the economical requirements, hence avoiding any last minute monetary issues [4]. They can also aid in preparing effective treatment plans for patients, as their stay length is predetermined [5]. Early interventions could be provided to avoid hospital acquired infections. Initial estimation can also aid in planned early discharge and planned at-home treatments [6]. In-patient stay levels can be identitifed and can be used to determine the requirements [7, 8]. Such measures not only benefit patients economically, but also aid them psychologically. Further, it helps in better management of communities and reduced hospital waste [9].

Several problems and complexities prevail in accurately determining the length of stay factor. The major complexity lies in perfectly determining the features to be used for the prediction process [10]. Base data used for the process is obtained from hospital records. Hence it is usually textual in nature and contains several duplicated entries [11]. They are also divided into several sections based on the department from which the data is obtained. This results in too many available parameters. The major issue is that their complexity is not completely understood, as the parameters are textual in nature [12]. Further, the interplay between the parameters are also to be analyzed with utmost importance. This leads to difficulty in developing a generic system [13]. This work proposes an effective model that aims to provide a generic system that can accurately predict the length of stay of patients. The proposed Data Engineering and Ensemble based LoS (DEEL) prediction model is divided into two major sections; data engineering, and model building. The data engineering section performs a deep analysis of the available parameters to build the training data, and the model building section creates a boosted ensemble model for prediction. Experimental results and comparison indicate highly effective performances, indicative of the suitability of the model to be used in real time. The remainder of this paper is structured as follows; section II presents the related works, section III presents a detailed view of the DEEL model, section IV presents the performance evaluation, section V presents a comparison study, and section VI concludes the paper.

Related works

Predicting LoS in hospitals serves as one of the major components dealing with sustainable operations. Several works have been proposed in this domain. A data analytics based model that uses a deep learning network for prediction was proposed by Zolbanin et al. [14]. The work stresses the significance of feature creation using historical data of patients. The results obtained from the model shows a tolerance level of ±3 days. A length of stay model used for ICU patients was proposed by Ma et al. [15]. This technique operates on a hybridized just-in-time learner and a one class Extreme Learning Machine (ELM). The model uses a threshold of 10 days to discretize values of LoS attribute. Although the model exhibits good performances, ELM is computationally intensive, and when combined with high dimensional data, the model is not suitable for usage in real-time environment. A risk prediction model that is based on the patient's length of stay was proposed by Singh et al. [16]. This work uses a combination of regression modelling and deep learning for the prediction process. Regression modelling is used for the prediction of length of stay, while deep learning models is used for the mortality prediction process. An extended stay prediction model was proposed by Burton et al. [17]. This work is based on multivariable logistic regression model, which also concentrates on effective generation of sociodemographic features.

Predicting length of stay for specific injuries has also been on the raise, as such predictions are more fine-tuned towards the disease and can be more accurate. Length of stay of burn patients has been dealt with, by Yang et al. [18]. This study analyzes the LoS component in three stages, admission, acute, and post-treatment. The study also analyzes two artificial intelligence based prediction models for analysis. Predicting hospital stay of older adults was

dealt with by Curiati et al. [19]. This work performs variable selection, followed by backward stepwise logistic regression for prediction. A length of stay prediction model concentrating on patients admitted due to community-acquired pneumonia was presented by Uematsu et al. [20]. The model concentrates specifically on prolonged length of stay. The work uses Logistic Regression as the base model for the prediction process.AnArtificial Neural Network (ANN) based model for prediction on patients with acute pancreatitis was proposed by Ding et al. [21]. The model is based on backpropagation based ANN for the prediction process. A work dealing with identifying length of stay of patients dealing with pulmonary disease was proposed by Wang et al. [22]. Other works dealing with specific injuries to analyze length of stay are, general surgery and internal medicine based models by Jimenez et al. [23], trauma based stay predictions by Clark et al. [24], psychiatric care by Hodgson et al. [25] and Lowell et al. [26].

Data Engineering and Ensemble based LOS (DEEL) Prediction

Length of Stay (LoS) prediction deals with predicting the number of days a patient would stay in ICU. Predicting the LoS value is a crucial component in determining the mortality state of the patient. Higher LoS values have higher probability of resulting in mortality. The challenge in prediction process lies in effectively preparing the training data for the prediction process. This work presents an enhanced data engineering and an ensemble based LoS (DEEL) prediction model for effective prediction of LoS.

Data Engineering

The input data is obtained from hospital records. Hence the records are usually split into various files. Each file corresponds to a certain department. Hence, the records usually exhibit high levels of duplications. The initial step is integration of data that can aid in the detection of LoS. This mainly corresponds to the admission details and ICU stay details. Patient related physiological information are also identified from the multiple files and are integrated to form a single unified data file. Integration is entirely based on the patient identifier, which serves as the key feature for identification of a specific patient.

The integrated training data contains several categorical entries. Machine learning models can only operate on numerical entries. Hence data engineering and data encoding techniques are applied to the data to generate highly relevant numerical features for the training process. Data pertaining to the age details of the patient are entered in date formats. This is converted to numerical data by identifying the age value using the date of birth object. In order to incorporate anonymity into the data, date of birth values are converted to future date values. However, relationship between the age factors is maintained. Hence, even though the calculated age parameter contains an unrealistic value for age, it is relative and hence will aid in the machine learning process. Another major parameter for feature engineering is the diagnosis attribute. This attribute records the diagnosis information of a patient. Although the parameter is highly useful, it is recorded from the doctor's notes, hence is textual in nature. Analysis indicates that the diagnosis attribute contains 15,241 distinct entries. Such high levels of distinct values indicate that the parameter is string, and can be ignored. However, domain knowledge indicates that the parameter is very essential and can prove to be a parameter with high correlation to LoS. Hence the attribute is analyzed and it was identified that 14,805 distinct values were recorded by less than 10% of patients. This shows that the data is either a rare disease or due to linguistic errors. Hence these labels are merged into a single label, finally forming 435 distinct categorical values for the diagnosis attribute. All other features like gender, admission type, marital status etc. were identified to contain considerably acceptable level of unique values. Hence they are directly encoded. One-hot encoding is applied to the features, and the numerical vector is identified. Length of stay parameter is a continuous valued attribute. Literature reveals that patients staying for less than 10 days have low probability of mortality, while patients staying for more than 10 days exhibit high probability of mortality levels. Hence length of stay parameter is discretized with 10 as the threshold value.

This completes the data engineering phase. At the end of this phase, all available data is converted to numerical entries. The training data created has been merged from various files, and has high probability of containing null values. The null values are imputed using mean based imputation technique. This marks the end of the clean-up process, and the data is available for the model building process.

Model Building

Base data for LoS prediction has been collected from hospitals, hence the data is raw, and cannot be used for analysis. Most of the data attributes have been engineered or encoded. Hence the data contains large number of features. Encoding results in further increase in features. The engineered data for this work is composed of 540 attributes. This huge attribute space results in curse of dimensionality. The large attribute space also increases the complexity of the data. Feature selection is not an option, as most of the attributes have been manually built considering the domain requirements. They represent personal and physiological properties of the patent, which are mandatory for the prediction process. A highly complex model is required to handle such complex data. Hence, this work proposes a boosting based ensemble model for effective decision rule building.

Boosted ensemble model is composed of two major components. The base learner, which is a machine learning model used for predictions, and the boosting process, which is the iterator mechanism used to reduce error levels in the prediction process. This work uses Decision Tree as the base learner.

Let *y'* be the first level predictions obtained by applying the training data to the base learner *DT(x).*

$$y' = DT(x)$$

The iterator mechanism begins by first identifying the error levels (*e*). The error *e* is identified by finding the difference between actual target class (*y*) and the predicted target class (*y'*). This is given by

$$e = y' - y$$

The identified error levels are integrated into the training model, and the instances over which the errors were created are identified. Weights pertaining to these instances are increased to provide higher significance to the entries. This is given by

$$y'' = DT(x) + e$$

However, the resultant model is not free from errors. Integration of errors and weight modifications results in errors at a different perspective. These errors are identified by considering the differences, as in the previous iteration. This is given by

$$e' = y - y''$$

The new errors obtained are again integrated into the model, and the process of prediction and error integration is continued until the model reaches a certain error threshold. This marks the end of the training process. Prediction is performed by data engineering and encoding the test data, and passing it to the trained boosted ensemble model. The resultant prediction is binary in nature, with 0 representing the length of stay to be less than 10 days, and 1 representing the length of stay to be more than 10 days.

Performance Evaluation

Simulation setup

The proposed DEEL model has been implemented using Python inJupyter Notebooks. Performance of the DEEL model has been measured by applying the model on MIMIC III clinical dataset [27]. MIMIC III is a single center database with information collected from patients admitted in critical care units in Beth Israel Deaconess Medical Center in Boston. The dataset contains details measured from demographics, billing, clinical measurements, medical history, laboratory tests and pharmacotherapy. The records are for a seven year period ranging from 2008 to 2014. The data contains details about 38,597 distinct patients representing 49,785 admissions.

RESULTS AND DISCUSSION

Experiments were performed over the data, and the confusion matrix has been obtained representing the prediction levels in terms of True Positive (TP), False Positive (FP), True Negative (TN) and False Negative (FN). Prediction metrics used for analysis includes True Positive Rate (TPR)/ Sensitivity, False Positive Rate (FPR), Precision, Specificity, Accuracy, G-Mean and Lift.

$$TPR\ (or)\ Sensitivity = \frac{TP}{TP + FN}$$

$$FPR = \frac{FP}{FP + TN}$$

$$Precision = \frac{TP}{TP + FP}$$

$$Specificity = \frac{TN}{TN + FP}$$

$$Accuracy = \frac{TP + TN}{TP + TN + FP + FN}$$

$$G - Mean = \sqrt{\frac{TP}{TP + FN} \times \frac{TN}{TN + FP}}$$

$$Lift = \frac{TP}{TP + FP} / \frac{TP + FN}{TN + FP + TP + FN}$$

The ROC curve is constructed by plotting FPR and TPR values in the x and y axes respectively (Figure 1). High TPR and low FPR levels represent effective predictions. The pivotal point of the ROC curve is expected to be in the top left of the chart. It could be observed from the graph that the DEEL model exhibits high TPR levels and low FPR levels. The area under the curve is also observed to be high, depicting effective performances. PR curve of the DEEL model is constructed by plotting Recall and Precision in the x and y axes respectively and is shown in figure 2. High values of precision and recall represent effective predictions. The PR curve shows very high values of precision at 0.99 and recall at 0.91. This exhibits the high efficiency of the prediction process.

Comparative study

A comparison of the performance of the DEEL model is performed with the one-class JITL-ELM model proposed by Ma et al. [15]. The model proposed by Ma et al. uses just in time learning mechanism integrated with one-class extreme learning machine, which is a variant of the artificial neural networks. Comparisons in Table 1 shows that the proposed DEEL model exhibits better performance in all the metrics except for Specificity. However, the increase in accuracy level at 8%, sensitivity at 30% and G-Mean at 5% indicates that the DEEL model exhibits exemplary performance. Further, the Lift levels show a reduction of 1.12, which also exhibits the high predictability of the proposed DEEL model.

CONCLUSION

Identifying the length of stay of patients has several advantages, including the ability to predict their mortality and administrative aspects of bed allocation. This paper presents a performance intensive DEEL model that aims to provide accurate prediction for the length of stay of patients. The proposed model is composed of two phases; the data engineering phase uses enhanced feature engineering and encoding strategies to create qualitative training data, and the model building phase ensures high prediction performances by creating a boosting based ensemble model. Experimental results and comparisons indicate highly effective performances of the DEEL model. Advantages of the proposed model is that it is generic, and can be used for prediction on any data. The work can be further extended by using natural language processing techniques to extract diagnosis details, and hence create a precise feature representing diagnosis. Further, the proposed model exhibits slight reduction in specificity levels, which could be enhanced by designing a model with better imbalance handling capability.

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27. Data Descriptor: MIMIC-III, a freely accessible critical care database

Table 1: Performance Comparison of DEEL and Ma et al.

	Ma et al.	DEEL
Accuracy	0.82	**0.9**
Sensitivity	0.614	**0.91**
Specificity	**1**	0.77
Precision	**1**	**0.99**
G-Mean	0.784	**0.83**
Lift	2.13	**1.01**

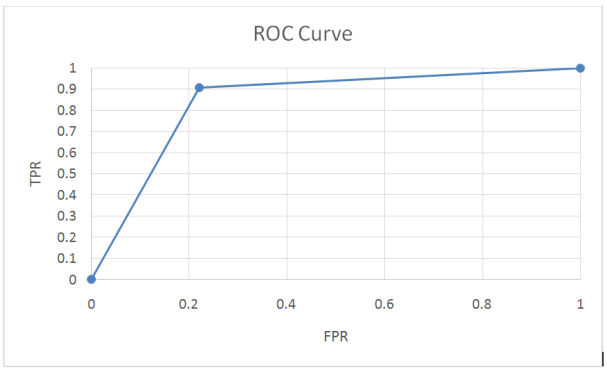

Figure 1: ROC Curve of DEEL Model

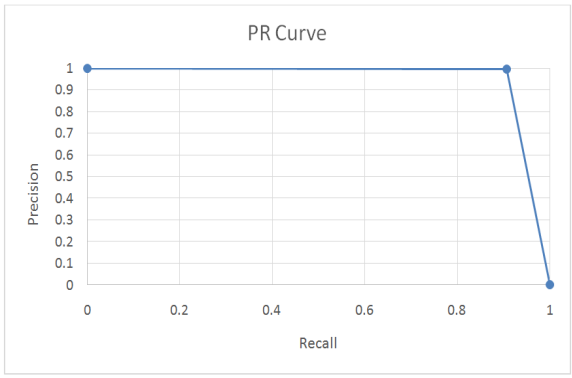

Figure 2: PR Curve of DEEL Model

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RESEARCH ARTICLE

Physico-Chemical Assessment of Ground Water Quality In and Around Rajakulam Pond, Dindigul City, Tamilnadu

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ABSTRACT

Ground water samples collected from different locations in and around Rajakulam pond Dindigul city during November of monsoon period (2019), were analyzed for physico-chemical parameters such as temperature, pH, TDS (total dissolved solids), electrical conductivity, total hardness, calcium (Ca), magnesium (Mg), sodium (Na), potassium (K) and chloride (Cl). Based on the various experimental results, it is arrived at the conclusion that the adjoining ground water sources are mostly affected and the water becomes very salty with very high TDS and that the ground waters are unfit for drinking purpose and some suitable treatments are necessary so as to keep the values of some parameters within desirable limits of BIS standards for drinking water. Hence the polluted water is suggested to water treatment using Reverse Osmosis System.

Keywords: Ground Water, Sewage, Industry effluent, BIS.

INTRODUCTION

Water is the precious gift of nature to all the living beings for sustenance. The suitability of water for domestic, agricultural and industrial purposes mainly depends on the chemical composition of surface and subsurface. Groundwater is the largest source of fresh water on the planet excluding the polar icecaps and glaciers. Groundwater is widely distributed and is used for domestic, industrial and agricultural purposes throughout the world. Groundwater is a valuable natural resource that is essential for human health, socio-economic development and functioning of ecosystems (Steube et al. 2009). The chemical composition of groundwater is very important criteria that determine the quality of water. Water quality is very important and often degraded due to agricultural, industrial and human activities. The quality of groundwater is getting severely affected all over India. Contamination of groundwater can result in poor drinking water quality, loss of water supply, high clean-up costs, high costs for alternative water supplies, and/or potential health problems (Balakrishnan et al. 2011). Therefore, determination of groundwater quality is important to observe the suitability of water for a particular use

(Arumugam & Elangovan 2009). Industry and agriculture discharge liquid waste product. Rain as it falls through the air or drains from urban areas and farmland absorbs contaminants serious incidents resulting from spillage or discharges of toxic chemicals from the pollution of river. Many industrial wastes discharged in to water mixtures of chemicals which are difficult to treat. Some industrial wastes are so toxic that they are strictly controlled, making them an expensive problem to deal with some companies try to cut the costs of safety dealing with waste by illegally dumping chemicals. Effluent irrigation has been practiced for centuries throughout the world (Shiva et al., 1986). It provides farmers with a nutrient enriched water supply and society with a reliable and inexpensive system for wastewater treatment and disposal (Feigin et al., 1991).

Scope and objectives of the study

The sewage from the houses located around the Rajakulam pond and also from other canals discharged the polluted water into the pond without any treatment. Hence the water quality in the pond is badly affected. The contaminated water from the pond seeps into the wells and bore wells and thus pollutes the ground water sources around the pond. Water becomes salty and unfit for any use. Hence there is a need to study the impact of sewage water in the quality of pond water.

Objectives

- To analyze the physico-chemical parameters of the Rajakulam pond water during monsoon.
- To analyze the ground water quality parameters in the water resources in and around the pond.
- To recommend suitable remedial measures for the treatment of contaminated ground water using REVERSE OSMOSIS TECHNOLOGY.

MATERIALS AND METHODS

The Rajakulam pond located at Karur road, near Trichy road belongs to Dindigul. The area of the pond is about 15.39 hectare. The pond capacity is about 0.9747million cum (or) 34.42million (FT).There are seven number of inlets adjoining in sewage water. The sewage from the habitant living around the pond at the distance of 10 km are discharged through the drain into the pond, which leads to the pollution of the pond, at an alarming rate. During rainy season, the rain water collects in the pond. The rain water is the main source of water to the wells and bore wells located around the ponds at a radius of 10 km. The rainwater collected in the pond is contaminated with sewage water, which percolate to the ground and reach the bore well and wells. This causes the pollution of the ground and well water, contamination makes the water very hard and salty, so the water becomes unfit for domestic and agricultural purposes. The polluted well and ground water used for agricultural purposes around the pond, this in turn affects the soil. It gets polluted slowly and become unfit for cultivation due to changes in the properties of the soil.

RESULTS AND DISCUSSIONS

Drinking Water Standards: Different agencies have set environment standards for safe drinking water as Bureau of Indian Standards (BIS), World Health Organization (WHO), and European Economic Community (EEC) etc. Drinking water standards are regulation that Bureau of Indian Standards (BIS) set to control the level of contamination in the drinking water. Bureau of Indian Standard considers the inputs from several organization i.e. Central, State, Semi Government, Municipal Corporation, Public Health Organization, etc. throughout the standard setting process.

Sensitive Parameters: Parameters like TDS, EC, total hardness, calcium, magnesium, Iron and chloride are taken as sensitive parameters to indicate the water pollution by industrial effluent from different sources. It is observed that in all the sampling sites in and around Rajakulam pond these values are high compared to the BIS Standards.

CONCLUSION

An attempt has been made to study the impact of untreated sewage water in Rajakulam pond located at Karur Road, Dindigul. In fact the sanitary wastewater comprises about 99.9 percent of water along with microorganisms. The pond water was used for bathing, washing and also agricultural purposes, but at present the pond has become the place for collection of sewage water from the houses located in an around the pond to a radius of 5 km. So the water is completely polluted and reaches an alarming degree of pollution. In order to evaluate the physical, chemical and microbiological parameters, the water samples from the pond, wells and bore wells from the residence located in and around the banks of the Rajakulam pond were collected. The physic- chemical analysis of water in the pond as well as the ground water sources around the pond reveals high turbidity. High TDS shows that the water cannot be used for domestic purposes. The electrical conductivity, total hardness, high chloride content in the pond as well as in the ground water sources indicates that the water cannot be used for human consumption. During the rainy season the rain water harvesting in the pond is essential to reduce the impact of sewage pollution by dilution. In order to improve the quality of ground water around the pond a suitable R.O system can be used to remove salts present in the well water.

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Analysis of the contaminated water

S.No	Parameter	Method of Analysis
1	Colour	Visual comparison
2	Turbidity	Neplo turbidity meter
3	TDS	Conductivity method
4	Electrical conductivity	Conductivity meter
5	pH	pH Meter
6	Total hardness	EDTA Titrimetric method
7	Calcium	EDTA Titrimetric method
8	Magnesium	Calculation from Total Hardness
9	Iron	Spectrophotometer
10	Ammonia	Nessler's Method
11	Nitrite	Spectrophotometer
12	Nitrate	Spectrophotometer
13	Chloride	Silver nitrate
14	Fluoride	Colorimetric meter
15	Sulphate	Turbidity method
16	Phosphate	Spectrophotometer

Comprehensive Table Water Quality Analysis

Sample collection	**BIS Limit**	**S1**	**S2**	**S3**
Appearance	-	Turbid	Slightly blackish	Slightly blackish
Color (Pt.Co-Scale)	5	Blackish	Slightly blackish	Slightly blackish
Odour		Objectionable	None	None
Turbidity NT units	5	18	16	12
Total dissolved solids mg/L	500	2826	4875	3206
Electrical conductivity in Micro mhos/cm		4685	7640	2773
PH	7.0-8.5	7.47	7.64	7.78
Alkalinity total as $CaCO_3$		540	640	480
Total hardness as $CaCO_3$ (mg/L)	300	1220	1920	1160
Calcium as Ca mg/L	75	140	200	143
Magnesium as Mg mg/L	30	58	71	53
Sodium as Na	_	320	200	168
Potassium as K	_	60	85	36
Iron as Fe mg/L	0.3	2.13	2.94	1.40
Ammonia as NH_3 mg/L	_	4.36	5.98	2.93
Nitrite as NO_2 mg/L	_	9.29	1.64	0.16
Nitrate as NO_3 mg/L	45	21	16	10
Chloride as Cl mg/L	250	390	350	290
Fluoride as F mg/L	1	1.2	1.0	1.0
Sulphate as SO_4mg/L	200	64	45	44
Phosphate as PO_4 mg/L	_	4.74	3.54	2.19
Tidy's test 4 hrs as O_2		7.55	5.06	4.33

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RESEARCH ARTICLE

A Systemic Review on the Importance of Herbs on Bad Clinical Outcomes of Drug-Induced Acute Renal Failure

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ABSTRACT

Acute kidney damage (AKD) is associated with adverse clinical outcomes and should be treated as a medical emergency. The International Guideline for the group on Kidney Disease Improving Global Outcomes (KDIGO) defined AKD as an increase in serum creatinine, decreased urine output, and a decline in renal function due to nitrogenous waste retention in the body. AKD development may result in intrinsic renal parenchymal disorders, renal flow contraction, or obstruction of urine. The primary challenge is medication toxicity, volume overload, and uremic consequences, among others. When medical therapy alone is insufficient to overcome a hurdle, kidney replacement therapy is performed; its mortality rate is about in patients with AKD, and numerous therapeutic techniques are now being evaluated in clinical studies.

Keywords : Pre-renal kidney injury, kidney failure, Nephroprotection, and Multi-organ dysfunction .

INTRODUCTION

Acute kidney injury (AKI) or acute renal failure (ARF) is a transient condition in which the kidney suffers damaged or fails, as indicated by the glomerular filtration rate (GFR), and occurs within few hours or days(1). It is a well-known complication associated with unfavorable results in persons in poor health (2). Globally, around one in five adults (21.6%) and 1 in 3 adolescents (33.7%) suffer from AKI (3). It is independently associated with increased mortality and morbidity. AKI is associated with chronic kidney disease (CKD) when there is an elevated risk of renal sequelae. Numerous reasons exist to lower the high mortality and morbidity associated with therapies and accelerates renal function recovery. Numerous research studies, including RIFLE (Risk, Injury, Failure, Loss, and

End-Stage), AKIN (Acute Kidney Injury Network), and KDIGO, indicate that (Kidney Disease Improving Global Outcomes). KDIGO is the most frequently utilized and most recent method of accumulating water, sodium, and various electrolyte imbalances (4). According to KDIGO, serum creatinine must increase by at least 0.3mg/dL (26.5µ mol/l) in 48 hours or by at least 1.5 fold from baseline within seven days (5). The flow of Urine output of less than 30 mL/hr (about 0.5 ml/kg/hour for a 70-kg patient) should be regarded with suspicion (6). As a result, it results in the dysfunction of critical organs such as the liver, brain, lung, heart, and gut due to abnormal communication of organ-organ communication (7). AKI was linked to the length of stay in the hospital, renal morbidity, and overall mortality; it is also stage-dependent. AKI stages are classified into three severity levels based on the magnitude of serum creatinine increases. Stage 1 (mild) through stage 3 (severe) is characterized by the magnitude of serum creatinine increases. AKI has a mortality rate of 40-50% when treated in the hospital. The death rate for ICU patients with AKI exceeds 50%, especially when AKI is severe enough to necessitate dialysis (8).

PREVALENCE

Asia is the world's most populous continent and the world's largest. Climate, culture, regional features, and development heterogeneity are all significant. Siberia's climate is arctic and subarctic, while South and Southeast Asia's climate is tropical. Eastern Asia had a KDIGO-equivalent rate of 19.4%, and Southern Asia had a KDIGO-equivalent rate of 7.5%, Southeastern Asia had a 31.0%, and Central Asia had a KDIGO-equivalent rate of 9.0% and 16.7% in Western Asia. Eastern Asia had a pooled mortality rate of 36.9%, Southern Asia had a pooled 13.8%, and Western Asia had a pooled mortality rate of 23.6% (9). There are numerous clinical conditions, including circulatory shock, radio contrast agents, critical illness, sepsis, and nephrotoxic medications or radiocontrast agents (10). Despite this, the problematic clinical course associated with the etiology of AKI has increased the demand for the development of new pharmacological agents (11).

NATURAL PLANTS ARE ESSENTIAL FOR NEPHROPROTECTION.

However, readily available natural remedies such as ginger, garlic, grape, pomegranate, saffron, and ginseng are helpful against several models of acute renal failure (12). Additionally, several well-known Traditional Chinese Medicine (TCM) remedies have been frequently utilized to treat AKI. TCM has been extensively studied in animal models and even on humans to determine its therapeutic efficacy. The following are some of the herbs that are protective against drug-induced nephrotoxicity were shown in (Table-1).

ETIOLOGICAL FACTORS

The kidney's higher considerations include urine filtration in the glomeruli, which is reabsorbed in the proximal tubules, and the fluent accumulation of metabolites and drugs. For this reason, drug-induced injury is hazardous to the kidney (43). The essential urine is concentrated in the proximal tubules and filtered through the glomeruli (44). A new kidney abnormality or a malfunction caused by drug medicaments is referred drug-induced kidney injury (45). Additionally, the threat is more significant in patients who are elderly, dehydrated, overuse drugs, have impaired renal function, or have baseline diseases such as multiple myeloma or hyperglycemia. An analgesic or antipyretic medications, immunomodulatory, antibiotics such as new quinolones, aminoglycosides, anti-cancer drugs, i.e., Cisplatin, vitamin D, calcium preparations, and drugs for high blood pressure (RAAS blockade), are the medicaments that frequently cause kidney dysfunction (46). Acute kidney injury (AKI) is a prevalent and severe health complication characterized by frequently demanding clinical disorders and a high mortality and morbidity rate. As one of the world's largest continents and with the world's largest population, Asia is critical for eradicating AKI. Climate, customs, economic status, and other factors contribute to Asia's distinct clinical manifestations of AKI. It demonstrated the vast economic and medical implications of AKI on Asian continents by comparing the clinical characteristics of AKI indistinguishable Asian countries and the clinical environment. AKI is frequently caused by drugs or sepsis. Despite this, insufficient documents have been resolved (47). AKI affects humeral, immunologic changes, and hemodynamic, which directly results in abnormal functioning of distant organs, including heart, lung, brain, liver, intestine, and immune system (48). The effects of acute renal injury (ARI) on distant organs are shown in (Fig-1).

DISCUSSION

Prerenal, intrinsic, and post-renal causes of acute kidney injury are the most common [49]. One of the causes of prerenal acute renal damage is decreased hypovolemic flow, as occurs during shock. For example, there is a decreased efficient circulatory volume in congestive coronary heart failure or liver failure. These factors contribute to decreased glomerular filtration [50]. Another possibility is impaired renal autoregulation due to the use of neurotoxins, such as NSAIDs, which cause vasoconstrictions of the afferent arterioles, resulting in decreased hydrostatic pressure decreased glomerular filtration rate. ACE inhibitors or angiotensin receptor blockers cause vasodilation of the efferent arterioles. However, it is exacerbated by renal injury. Typically, prerenal injury is reversible [51]. Prolonged prerenal injury, on the other hand, is frequently an ischemic injury. AKI is the primary cause of renal dysfunction. It is classified as glomerular nephritis (inflammation of the glomerulus), nephrosis, and various causes. The tubular disease is the central acute tubular necrosis caused by prerenal acute kidney injury [52]. Other tubular diseases are frequently caused by infections that affect tubular cells or by nephrotoxins. Interstitial disease, which includes acute interstitial nephritis, can also occur due to ischemia infection, animal tissue disease, or the use of nephrotoxic or near toxin [53]. Vascular disease encompasses vacuities and microangiopathic hemolytic anemia, both caused by substances TTP. Post renal acute kidney injury is also known as post-obstructive acute kidney injury. It is essential obstruction anywhere along the track from the pelvis to the ureter bladder to the urethra is caused by renal stones, which may obstruct the ureter, resulting in ureter dilation, referred to as hydronephrosis. Prostate enlargement, prostatic adenocarcinoma, cervical cancer, and bladder cancer are additional causes. Internal causes of acute kidney injury can include obstruction or infection. It damages the nephrons, increasing serum creatinine [54]. Acute kidney injury is frequently unknown at discharge because patients require local awareness to avoid future kidney function loss. Specifically, AKI survivors account for less than half of patients aware of the risk of common nephron toxins, such as NSAIDs, impair recovery or increase the risk of recurrent AKI. The majority of patients who have severe AKI were unable to identify common nephrotoxic drug exposures reliably. However, it could be improved by communicating with clinical experts and expressing a desire to learn more about AKI and its complications in the patient's overall health [55]. Knowledge about AKI and its relationship to future outcomes is also warranted, as education-specific interventions can improve outcomes.

CONCLUSION

AKI may be a widespread global problem that has imposed an unrecognized global burden thus far. It is critical to raise awareness of AKI and arm caregivers and patients with the knowledge and tools necessary to identify and appropriately manage patients in danger. A thorough understanding of pathophysiology will result in novel approaches to diagnosis and treatment, ultimately resulting in kidney preservation. While renal replacement therapy is beneficial, it is not the first line of treatment for AKI, particularly in cases of preserved diuresis. While the kidney is a miraculous organ, it is frequently overwhelmed when pushed to the limit. We should always make an effort to maintain kidney function.

CONFLICTS OF INTEREST

All authors have equal contribution

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Table 1. List of Nephroprotective Plants

Common Name	Order/ Family	Therapeutic Uses
Desert cotton	Caryophyllales	Nephro protective (13)
Mountain knot grass	Caryophyllales	Antiurolithiatic property(14)
Orchid tree	Caesalpinioideae	Nephro protective (15)
Avarike	Fabales	Urinary tract diseases Liver diseases (16)
Pappaaya	Brassicales	Urinary tract diseases(17)
Locust bean	Fabales	Nephro protective (13)
Autumn squash	Cucurbitales	Antiurolithiatic property(18)
Bell mimosa	Mimosoideae	Nephro protection(19)
Bodhi Tree	Artocarpus	Urinary tract diseases Liver diseases (20)
Sausage Tree	Lamiales	Antiurolithiatic property(21)
Garden cress	Cruciferae	Hepatoprotective &Nephro protective (22)

Ninjin	Apilales	Urinary tract diseases Liver diseases (23)
Kutki	Lamiales	Antiurolithiatic property(24)
Seashore mempari	Papilionoideae	Nephro protective property(25)
Red sage	Lamiales	Antiurolithiatic property(26)
Little ironweed	Asteraceae	Nephro protective (27)
Indian baels	Sapindales	Urinary tract dysfunction &Liver diseases (28)
Varuna	capparaceae	Antiurolithiatic property(29)
Amloki	Euphorbias	Hepatoprotective &Nephro protection(30)
Black sugar	Fabales	Urinary tract diseases Liver diseases (31)
Talikmkhana	Acanthaceae juss	Nephro protective (32)
Canthedral bells	Saxifrages	Antiurolithiatic property(33)
Mulberry	Gentianales	Hepatoprotective &Nephro protective (34)
Kalonji	Ranunculales	Urinary tract diseases &Liver diseases (35)
Holy basil	lamiaceae	Nephro protective (36)
Java tea	lamiaceae	Antiurolithiatic property(37)
Harmal	Gentianales	Nephro protective (38)
Makoi	Solanales	Urinary tract diseases (39)
Thethankottai	Gentianales	Nephro protective (13)
Caltrop	Zygophyllales	Antiurolithiatic property (41)
Winter cherry	Solanales	Nephro protection(42)

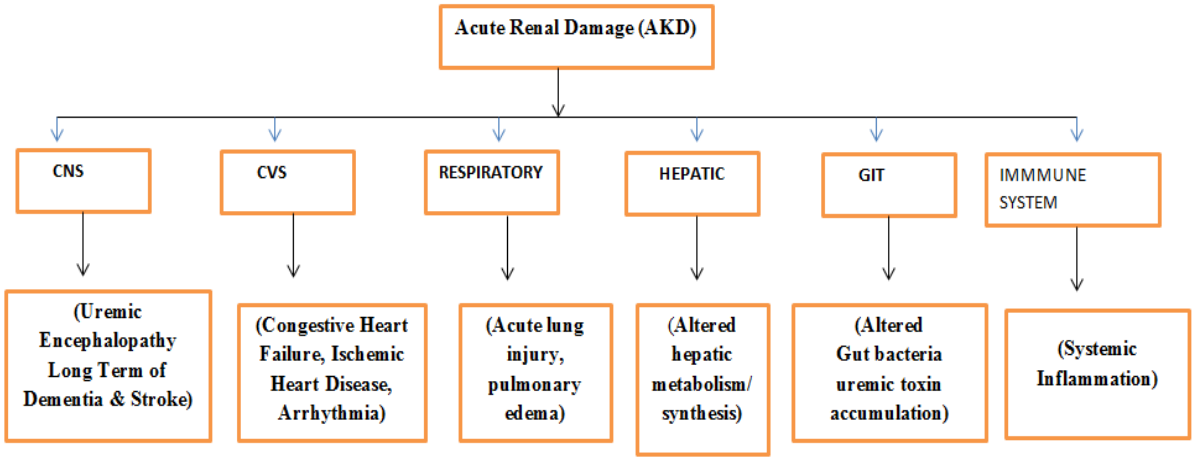

Figure 1. Acute renal damage cause multi organ dysfunction

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REVIEW ARTICLE

A Review on Nanocoating Techniques for Corrosion Resistance on Various Metallic Surfaces

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ABSTRACT

Corrosion cause a severe structural damage on component surface and this will create a clot in operation, performance and finishing of the process. This problem may be protected by various techniques utilized in industry. Now a days Nanocoatings are effectively utilized to prevent corrosion on various components of the structure. Nanocoatings provides many advantages includes surface hardness, strength, high temperature resistance etc.. Nanocoatings can be applied in thinner as well as rough surface also. A Nanocoatings is a process of coating which has stimulated in the nanoscale. Utilizing of micro structure coating method can prevent the corrosion, but not upto the mark. This paper briefly reviews about various Nanocoating techniques such as Titanium oxide coating, Zirconium Nanocoating, ceramic Nanocoating, Nanocomposite coating, polymer matrix Nanocomposite coating and Electroless nickel Nanocomposite coating that can be applied to various components and structures in the industry in order to prevent the components from the corrosion and improving the corrosion resistance.

Keywords: structural damage, Nanocoating, high temperature resistance, titanium oxide, zirconium.

INTRODUCTION

Corrosion is the one of the major thrust area in research, which is recognized as a problem causing degradation, failure of the component and series accidents in industries including aviation. Corrosion is the deterioration of the components or parts due to their reaction with corrosive element in their surroundings such as oxygen and carbon dioxide etc…damages due to corrosion leads to many problems includes repair and maintenance, lost of components, decrease in efficiency and so. Corrosion is a process which leads the dissolution of the material with

respect to aggressive environments. The affecting factors of the corrosion is mainly depends on the material and environmental condition. Corrosion can be happened in different ways including of uniform, galvanic, crevice, pitting and erosion etc.. corrosion in the form of uniform is most incidents and having affected and wasting in large amount. The remaining corrosion forms are localised and also not affected and wasting combatively with uniform form of corrosion.

Corrosion can greatly compromise the strength and integrity of the various aircraft components. This may be protected by introducing new composition to base element, creating a corrosion resistance alloy, surface coating, when the protection get fails, a corrosion in different forms will be developed and the form of the corrosion is purely depends upon the material involved, its size and shape, its specific function along with environmental conditions. Prevention of corrosion is performed through different techniques and choosing of methodology is most important for every material or component. Corrosion can be prevented by (1) Material selection, which one is relatively unreactive (2) obeying the environmental conditions, such as the addition of inhibitors, (3) compensating surrounding temperature (4) decreasing sulphur, chlorine and oxygen content (4) cathodic protection, where the corrosion current is forced to flow to the component or surface in order to protect the component. Coating is the most preferable method preventing and controlling the corrosion due to an available for different conditions and applications. Coating it may be inner or outer surfaces can be applied for different range of temperature. Coating technique may have high cost but it is a suitable method for long term and large scale industries including aviation for its natural resources, safety, life of the equipment etc.. recently nanomaterials play a wide role to reduce and control corrosion. Nanomaterials are materials at least one of the their features are in Nano scale(less than 100nm) and they will be available in zero dimension, one dimension, two and three dimension.

Role of Nanocoating in corrosion control

A Nanocoating is a process where all the constituents are less than 100nm and they undergone a high density of grain boundaries[1]. Nanocoating have been classified based on the constituent materials[1,2]. Nanocoating have one part that is in nanoscale. Due to the fine size of the particles of Nanocoating blocking the corrosive elements is more efficient when compare to other technique. Based on the adhesion properties from grain boundaries, the lifetime of the coating will be increased[2]. It will provide high mechanical as well as electrical properties, which will make more stronger and harder. Nanocoating technique is familiar for its self-healing, self cleaning and wear resistance. Particularly in aviation industry, Nanocoating technique is highly preferred for its extraordinary properties like flame-retardant, corrosion resistance, and electrically conductive [1,2,3]. Application of Nanocoatings by three methods namely mechanical, physical and chemical deposition [1,4]. Mechanical deposition can be applied through spray, painting and dip coating. Physical deposition can be applied through bonding and condensation. Finally chemical technique involves low cost but requires expensive precursors [1,5]. The technique must be applied according to the optimised condition in order to attain best result of Nanocoating in the form of uniformity, smoothness, adhesion, crack-free surfaces etc.. it is a effective barrier for high temperature applications especially aviation power plant where high temperature generated. The rate of corrosion is plotted by penetration rate, which is the thickness loss of the material per unit time[4]. It have expressed in different units such as mpy (miles per year), mm etc.. for typical ferrous and alloys outstanding corrosion resistance margin is below 0.02. and the Nanocoating corrosion behaviour is affected by different parameters such as environment, substrate and composition. The corrosion have been classifies as either direct chemical attack or electrochemical attack.

Advantages of Nanoparticles as well as Nanocoatings

The advantages of Nanoparticles includes (1) particle size and surface characteristics of nanoparticles is easily changed to flow (2) they control and sustain during the localisation (3) site specific target can be achieved through high density properties and grain boundaries (4) increase the lifetime of the component (5) prevent structural damage by resisting corrosion on the surface of the component (6) react with foreign objects in order to control the corrosion rate[3].

Metallic Nanocoating

It is a process of combination of just one or more pure materials, such as titanium, aluminium, iron, copper, zing etc.. it can be either pure material or alloy for enhanced performance invention. Sputtering and multi-arc iron plating is technique where frequently applied in aerospace industry for its high resistance properties[1,3,6].

Composition of Nanocoating

Choosing of metals in the Nanocoating is very important because it is improving the physical, chemical, electrical and thermal properties[1,3,4,7]. For example zinc Nanocoating overcomes weldabilty as well as surface finishing problems that arise when thickness need to be increased. Alloyed metals provide extraordinary properties instead of pure materials even at nanoscale[8].

Materials required

Aluminium sheet with the dimensions of 5 cm * 2 cm * 5 mm is used for development of hydrophobic surface and cleaned with drilled water. In aircraft fuselage, tail sections and vertical fin are made with metal construction by using the aluminium sheet. It is frequently utilized in majority parts of the aircraft because of its low weight. Liquor ammonia may be used as a complexant and base. Ammonia solutions are used for dissolving of silver oxide residues. Benzene is a organic chemical compound having 6 carbon atoms. The main function of benzene is to undergoes substitution reactions. Polystyrene is a synthetic polymer, which is used for clear, hard and brittle. It is most widely used plastic for its very good properties especially in aviation industry.

Components required

The zeta sizer is a instrument is used to measure three(particle size, zeta potential, molecular weight) characteristic of particles or molecules in a medium of liquid. With help of this instrument we can measure the above mentioned three parameters over a wide range of concentrations. NIBS technique used to measure a particle size and molecules from 0.6 nm to 8.7 microns. M3-PALS technique used to accurate measure of zeta potential in both of aqueous and non-aqueous dispersions. Static Light Scattering(SLS) is used to measure the molecular weight, which is required for multi-angle measurements. A small amount of spin coating material is usually applied on the centre, which is either spinning at low speed or nor spinning part. The solvent, which have applied is usually volatile and evaporates. The film thickness is purely depends on the rate of viscosity and concentration of the solution and solvent. X-ray Difractometer is a technique which is used to calculate spacing between layers of atoms, orientation of the single grain, unknown material crystal structure and geometrical parameters of the crystalline.

Titanium dioxides Nanocoating

Titanium dioxide is a ceramic materials and it is mostly preferable for Nanocoating for aircraft structures(mostly in fuselage, tail, pin sections) because of its excellent physical as well as chemical properties including self-cleaning, ultraviolet protection, high refractive index and high abrasive and corrosion resistance. The surface preparation technique of substrate and the deposition method plays important role in order to maximum result in application of such method[9]. In this method, TiO_2 nanoparticles have been deposited on the stainless steel surface by sol-gel method through hydrothermal post treatment process in order to increase the corrosion protection. By using the same technique three or four layers of titanium dioxide nanoparticles coating have been revealed for better corrosion resistance on the stainless steel surface. Through this uniform coating, decreased the corrosion current density by three times and increased the corrosion resistance by nearly 10 times[10]. The protection rate of corrosion of titanium was investigated to improve coating resistance by monitoring size of the particle and thickness of the nanofilm[10]. In order to achieve a high corrosion resistance of Nano titanium dioxide coated carbon steel, the sixe of titanium dioxide nanoparticles need to be decreased. Atomic layer deposition method gives the advantage of having a whole shield over the surface without any pinholes or cracks compared to other methods like physical vapour deposition, chemical vapour deposition etc[11].. forming of multiple layers will improve the resistance of Nanocoating, increase the susceptibility of deformation. While thickness of deflection is generated, it will reduce the performance on the corrosion resistance.

Nanocoating by Alumina

Nanocoating by alumina thin film is very popular on various metallic surfaces including aviation industry for its excellent mechanical properties as well as corrosion resistance. Alumina Nanocoating by preparation method was studied for its effect on the corrosion and reported a better corrosion resistance of 9Cr-1Mo ferric steel coated with Nanocoated sol-gel alumina Nanocoating compared to the uncoated steel[10]. ALD method was frequently used for its advantages of controlled, smooth and equally coated surface. With this method the deposition temperature is achieved upto 500℃. For example Nanocoating of alumina gives a better corrosion resistance for coating with ALD at 250℃ compared to the same materials which one prepared at 160℃[13]. High temperature reduce the level of porosity and increase the sealing performance of coating. Carbon steel should be deposited at lower or room temperature for not affecting its structure. The alumina Nanocoating is deposited on 100Cr6 carbon steel with ALD method at 160 ℃ and thickness of the coating needs to be more than 10nm to prevent corrosion[12]. The alternative method for achieving of good level of sealing at room temperature is plasma-assisted ALD (PL-ALD) method. This technique involves oxygen radicals in the process, to achieve a higher level of sealing at room temperatures without long purging times. An excellent adhesion properties and corrosion protection of the film was reported with PL-ALD for aluminum alloy and 100Cr6 steel.

Nanocoating by Tantalum oxide

Pentoxide is a metal, which exhibits excellent physical, structural, optical and electrical properties such as high dielectric strength, hardness and chemical attack resistance under severe conditions[15]. Coating of Ti- 6A1-4V alloy with ß-Ta_2O_5 gives a stable passive film on its surface. Meanwhile tantalum nitrate showed a decrease in corrosion resistance with increased acidity and temperature.

Nanocoating by Zirconia

Zirconium coating is used for many industrial applications in thermal barrier coatings, metal corrosion protection, optic devices and magnetic storage etc.. it is practically implemented as a coated material due to its high corrosion resistance, high melting point, long life and high temperature resistance. Zirconium thin films will be deposited through various methods like (1) sol-gel (2) hydrothermal process (3) thermal spraying (4) electro deposition and (5) ion-beam induced chemical vapour deposition. However sol-gel method is a best suitable method for large and complex surfaces along with higher degree of purity can be achieved by this method. By using sol-gel method, it is formed a enhanced rate of corrosion for 316L stainless steel in both acidic and neutral medium. It will increase the corrosion protection by decreasing the porosity, Penetration of the aggressive irons. At low frequencies one time constant was derived Zirconia Nanocoated at 500ºC, through the corrosion resistance was controlled by double-layer capacitance. The performance of the coating is purely based on the method of preparation[17]. Hydrothermal deposition is mostly preferred in industrial applications for its simplicity[18]. However spray pyrolysis is used to manage large areas for thin films at low cost, but is difficult to get homogeneous films. From this, choosing of right method is very important to attain a continues and compact Zirconia layer.

Other ceramic Nanocoatings

Coating by Graphene layers showed a better corrosion resistance than the organic once, which one have more than five times thicker[17]. A multi-layer Graphene coating on nickel surface performs 20 times slower than that of bare nickel.

Nanocomposites coating

It is a material composed of at least two immiscible phases, which have separated by an interface region. Matrix is a Dominant part, which one in increased the material properties. It may be metallic, ceramic or polymer but only condition is the dimension should be larger than the nanoscale. Nanocomposites coating is classified purely based on the filler type and it may be available in 0D, 1D, 2D nanoscale[18]. Combination of thin layers at nanolevel thickness of two or more different class materials form the laminate Nanocomposites. The main advantage of using Nanocomposites coating is to improve mechanical properties along with increased corrosion resistance[19].

Polymer Host Matrix of Nanocomposites coating

Polymer Nanocomposites coating have provided high corrosion protection due to its extraordinary properties they can offer[11]. Polymers are used as a host matrices for various composite films as a filler or pigment. In the polymer matrix, nanofillers are used to achieve a increase of stiffness, strength, conductivity and thermal resistance[12]. Using of ceramic nanofillers into a polymer matrix for improving the hydrophilic, anti-wear and self-healing properties which are probably increase the corrosion resistance[13]. Polymer Nanocomposites processing is highly difficult to proceed. Enhancement of the properties is purely based on the perfect dispersion and distribution of nanofillers in the matrix. It is noted that, many type of fillers are used to incorporate with polymers[19]. MWCNT, $A1_2O_3$, Graphene Oxide, ZrO, SiO_2, were added to epoxy and vinyl chlorine, epoxy resins and fluoropolymer matrices respectively for the purpose of corrosion protection. When Aluminium oxide nanoparticles blended mixed with the polymer, the mechanical properties will be strengthening to sustaining the corrosion resistance in the polymer itself. The introduction of GA and oleic acid (OA) to the chitosan to generate a Nanocomposite coating of CS/GO-OA will improve the corrosion protection than carbon steel in an NaCl solution. A hybrid Nanocomposite coating which consists of Graphene oxide-Zirconia oxide/ epoxy (GO-ZrO_2/EP) was prepared and then proceed for coating over a steel sheet[20]. The results showed that, adhesion strength will be improved and best result will be obtained when composition was made and a hybrid coating gives highest strength in resistance when compared to other elements such as EP,GO-EP,ZrO_2/EP coatings. It was notified that, corrosion resistance have been improved upto the addition of 5% concentration of the SiO_2. Nanocomposite coating can greatly reduce the corrosion[21]. Reduction of oxygen in the surface of the polymer will give low over potential areas and reduce the corrosion reactions in the surface.

Conductive Polymer Matrix Nanocomposite Coating

Conductive polymers are popular for their excellent electrochemical properties and they will be used as a host matrices in various composite films[22]. It was proved that, the presence of conductive polymers will greatly improve the corrosion resistance of the Nanocomposite coating. The commonly used conductive polymers are include of Polyaniline (PANI) , Polythiophene and Polypyrrole[1]. The PANI Nanocomposites improve the resistivity of the coating. 100 times improvement have been achieved in corrosion resistance through a PANI-TiO_2. The advantages of the conductive polymer Nanocomposite coating are include diffusion resistance, prevent charge transportation and incremental in surface area. When PANI integrated with $CaCO_3$, it is notified that, the corrosion rate was decreased[3,4]. The combination of TiO_2/GO showed better stability in seawater than the coating of polyvinyl alcohol/ Polyaniline[4,7,19].

Waterborne Polymer Nanocomposite Coating

The combination of polymer based waterborne coating with nanoparticles such as Fe_3O_4, Fe_2O_3, ZnO, were studied for behaviour in corrosion resistance[1,9]. It is examine that, adding of a small concentration of nanoparticles can greatly reduce the corrosion rate along with UV resistance[7], scratch resistance and abrasion resistance of the coating. A physical barrier would be formed by the epoxy coating in order to control the aggressive spices and metal surface protection with alloys also[18,23].

Metallic Host Matrix Nanocomposite Coatings

Various types of nanoparticles were mixed with nanocrystalline metal matrix coating such as silicon carbide, titanium dioxide and alumina to prepare Nanocomposite coating[1,2,5,6]. Addition of these nanoparticles to nickel and nickel alloy coatings will result in enhancement of corrosion resistance. For example, coating of SiC nanoparticles with Ni, Ni-W or Ni-Co alloys, corrosion resistance will be increased, when concentration of SiC increases. Furthermore friction force effect on SiC- Ni Nanocomposite have been examined in K_2SO_4 solution.When Aluminium oxide nanoparticles were mixed with nickel coating with steel and shows a better result in corrosion resistance improvement. Aluminium oxide act as a insulator on the surface of the composite, where better resistivity is determined in sodium chloride solution. The type of electro deposition coating and concentration of aluminium oxide nanoparticles were play a wide role in the corrosion resistance study[15]. Both the sediment co-

deposition(SCD) and adopting conventional electroplating (CEP) have been used with different nanoparticles concentration. CEP technique shows a better result in corrosion resistance compared to SCD[1,16].

Metal nitrate films preferred for their superior mechanical properties and corrosion resistance as protective layers. These files either in binary or ternary nitrate Nanocoating[1,13]. Ternary coating applied at high temperature (above 700ºC) if they do not degrade into porous oxides. for example, Cr-Al-N films are ternary films and they can provide oxidation resistance upto 900ºC. To increase the hardness and decrease the thermal conductivity, it is good to combine both aluminium with CrN Nanocoating. Titanium nitrate is a another type of ternary nitrate, which is used to apply to gas turbine compressor blades to reduce erosion effect. And addition of this titanium nitrate to Cr to improve the corrosion resistance and erosion performance, decrease the coating roughness and increasing coating density.

Electroless Nickel Nanocomposite coating

Particularly in a highly corrosive environment, to improve a corrosive protective layer Electroless nickel coating is the best suitable solution[25]. It is examined that, incorporation of TiO_2, Al_2O_3, SiC, SiO_2, nanoparticles with Ni-P matrix will have higher corrosion resistance. Depending on the nanoparticles incorporation, heat treatment have two opposite effects[26]. The increment of corrosion resistance by the TiO_2-Ni-P was examined that, it is based on the type of surface and its concentration. A higher rate of deposition will be reached with the addition of dodecyl sulphate (SDS) and dodecyl trimethyl ammonium bromide composition.

RESULT AND DISCUSSIONS

Compare to micro material coating, Nanocoatings provide superior enhancements in corrosion resistance and surface finishing[1]. Nanocoatings act through different mechanism to enhance the corrosion resistance and some cases they will improve the adverse effect. On the surface of the material a uniform physical barrier will be formed by fine size of the nanoparticles[2]. Compare to micro structures Nanocrystalline structures have superior properties for corrosion resistance due to its fine grain size, which will provide a higher integrity of the coated surface[1,3,4,9]. While applying a Nanocoating, it makes harder the surface, tougher and improves adhesion properties but coating thickness and composition should be designed according to the erosion decrease[12]. Due to high density of the grain boundaries, nanoparticles provides improved adhesion characteristics[15].

Nanocrystalline Ni and its alloy have a good promotion for metallic coating[1,4]. 13 -18 wt% of nickel in Zn-Ni alloys was proved the best corrosion resistance[6]. With a composition of around 8-12 wt% improves the corrosion behaviour by addition of phosphorus[22]. It was studied that, composition of Nanocoating, will dominate the grain size effect. Compare to the former technique, which produces a finer surface through direct current, pulse electro deposition provides better corrosion resistance[1,26,27]. Alumina Nanocoating was showed a enhanced corrosion resistance when it is composed with a plasma enhanced ALD technique[17,19]. Surface properties and corrosion characteristics improved through pre-treatment processes. It is examined that, titanium oxide and tantalum oxide has a higher corrosion resistance than the Zirconia and alumina. In addition to that, Zirconia has a potential to replace toxic chromium in the process[28].

Nanocomposite coating have a great advantages inclusion of cohesion and adhesion properties to form a strong bonding between structures, hydrophobicity, dispersion and distribution properties[1,29,30]. It is studied that, Nanocomposite coating corrosion behaviour is based on the synthesis method, type, concentration filler and heat treatment[21]. Titanium dioxide, silicon carbide and silicon dioxide has a positive corrosion behaviour when composed to the Ni-P matrix of a sodium chloride solution for Electroless coating and aluminium dioxide proved a good corrosion resistance when composed with in Ni matrix[16].

CONCLUSION

Stability and durability of the material is purely based on the corrosion resistance. Fundamental mechanisms of the corrosion process was gathered through the studies. Nanocoating influence the surface of the material in the aspects of structure, grain size, porosity, distribution of particle, surface etc...for example, the fatigue performance will be increased by the smooth surface, which will also increase the pit initiation. Excessive smoothness may also weak the coating adhesive and cause the detachments. If surface roughness decrease, it will increase the intergranular corrosion. Oxide formation on the surface is affected due to nanomaterials, hence transition mechanism will be difficult to detect the process and surface. Ions causes pit initiation and coating may isolate physically. To understand this transition mechanism, a deeper corrosion research is continuously required.

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RESEARCH ARTICLE

A Single-Phase Z-Source Charger with Soft Switch Modulation for Electric Vehicle Application

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ABSTRACT

A modulation is suggested that can carry out numerous Zero-Voltage-Switching (ZVS) and Zero-Current-Switching (ZCS) transitions with no auxiliary circuit. Despite having two hard-switching turn-off transitions, they happen at low current levels. The quasi-Z-source network may be switched on using ZCS. The quasi-Z-source network uses BCM or DCM operation to enable all free-wheeling diodes to switch off automatically. In addition, the current and voltage stress on all switches is the same as hard-switching. Thus, it is concluded that the new modulation makes the qZSC system much more efficient. Operational concepts for this soft-switching qZSC are explored.

Keywords : ZVS, ZCS, BCM, DCM, qZSC

INTRODUCTION

A recent wave of work has been focused on EV battery charger development with regards to on-board charging types. Using this usual charger for EVs results in more weight and more space. For these issues, academics have given attention to integrated chargers. This integrated charger shares DC/DC converter and control circuits with the EV system. to ensure the correct functioning of the integrated EV charger system, a bidirectional dc/dc converter is required. Direct Current/Direct Current Converters (DC/DC) Single-phase half-bridge, single-phase full-bridge, or three-phase full-bridge[1-5]. Concerning the Z-source network, it is possible to use bidirectional power flow, as discovered by F.Z. Peng in [6]. This inverter has recently been utilised in EV traction systems [7-8]. This article introduces a single-phase integrated EV charger called a quasi-Z-source network from [9] and incorporates it into AC

Propulsion Inc.'s vehicle industry. Fig. 1 depicts the architecture of this single-phase quasi-Z-source integrated charger. Another topology is given in [10]. In traction mode, the mechanism uses Sw. When the system is charging, Sw is switched off. The quasi-Z-source network acts as a buck converter in charge mode. With regard to the system total losses, it is essential to minimise this loss in order to improve overall system efficiency. Using soft-switching technology for the qZSC is critical.

Some methods to resolve the hard-switching issue are suggested. In [11], all devices, including switches and diodes, use ZCS to turn on and off. While this technique requires a connected inductor, capacitor, and diode. So as a result, enhance size and weight. [12] proposes another paired-inductor soft-switching quasi-Z-source inverter. The system only achieves bidirectional energy flow with one more diode added. The bidirectional soft-switched quasi-Z-source inverter [13-15] is suggested. For gentle turn-on or turn-off, two bidirectional switches are required. The primary switch achieves quasi-ZVS. All switches are switched on and off using ZVS. It has an auxiliary circuit that comprises an IGBT switch and two diodes. The topology is too complicated. In a soft-switching quasi-Z-source inverter, just one auxiliary switch is required. all switches including the auxiliary switch are zero-voltage switched on [16-17] suggests a resonant circuit for use in Z-source. Only the ZCS switches may be turned off. Two snubber capacitors provide soft-switching capability utilising separated quasi-Z-source converters. It has a low propagation loss. a gentle modulation for three-phase Z-source rectifier [18] ZVS enables the switches to be turned off using the diodes. It cannot do complete soft-switching. The suggested modulation, which doesn't require any auxiliary circuit, is called ZSVM3. And all major switches and diodes may be controlled remotely. In comparison to BCM and DCM, the ripple current is large. None of these approaches will result in a fully soft-switched design. This won't work with the integrated EV charging system. Fig. 4 illustrates a novel soft-switched modulation scheme for single-phase qZSC. This qZSC comparable architecture is illustrated in Fig. 2. There is no extra circuit, just a Z-source inverter/charger architecture. All primary switches have the ZCS and ZVS criteria applied. S7 is on with ZCS, and all free-wheeling diodes may be switched off. There is no voltage and current stress on all switches. Integrated EV charging system—so the suggested modulation is appropriate.

OPERATION PRINCIPLE AND ANALYSIS OF THE NOVEL MODULATION

Proposed modulation for single-phase qZSC

It has been suggested that the Z-source/quasi-Z-source network exists, which has motivated the authors to offer various modulation schemes for the qZSC/ZSC and quasi-Z-source inverter (qZSI)/ZSI. This range of space vector modulations for Z-source/quasi-Z-source networks includes ZSVM2 [20-22], ZSVM3 [19], ZSVM4 [23] and ZSVM6 [24]. However, single-phase qZSC should not use these modulations. A new modulation has been suggested for single-phase qZSC. This modulation is unipolar asymmetrical double-frequency modulation [25]. Fig. 3 shows a typical asymmetrical unipolar double-frequency modulation. The modulation index for phase an is μ and for phase b is μ.

SIMULATION RESULTS

This portion verifies the soft-switching technology modulations in a 1.3 kW PLECS setting. The 25% load model also works with the soft-switching technology. Simulation data are used to test all hypotheses. Parameters of qZSC in simulation model and prototype are same. Table I lists the prototype's parameters.

CONCLUSION

qZSC modulation with soft switching No auxiliary circuit is required. Using a new modulation, the inductor current is soft-switched to DCM or BCM. ZCS and ZVS can control all the switches in the Hbridge. 2S is switched off soft. Besides, all free-wheeling diodes are shut off in ZCS situation. The Z-source switch 7S is activated under ZCS conditions. In short, system efficiency improves as a result of decreased switching losses. The voltage stress and

current stress on all switches are on the same level. The soft-switching qZSC and unique modulation are appropriate for EV charging systems, making it more efficient.

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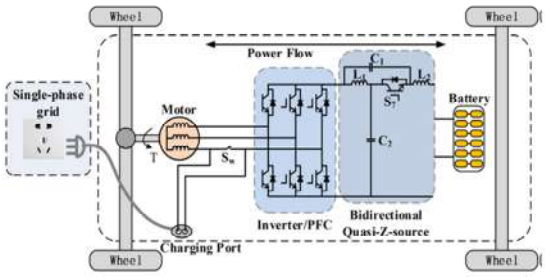

Fig. 1. The topology of single-phase integrated EV charger system

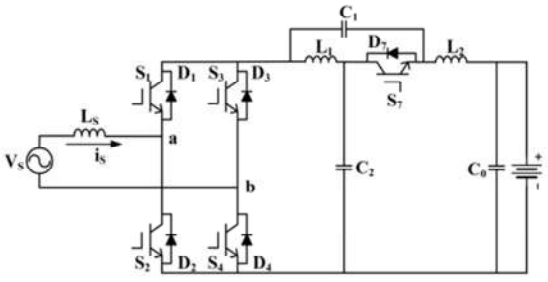

Fig. 2. The topology of single-phase qZSC

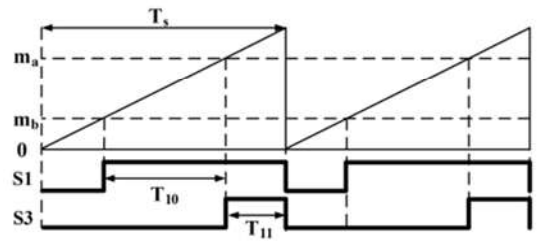

Fig. 3. Traditional asymmetrical module

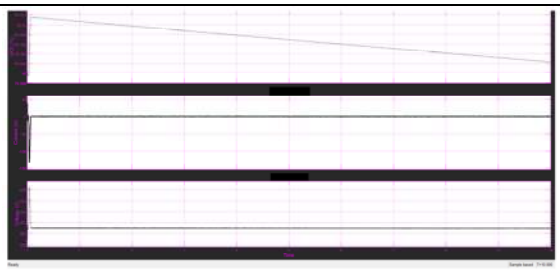

Fig. 4: Battery SOC, Current and voltage

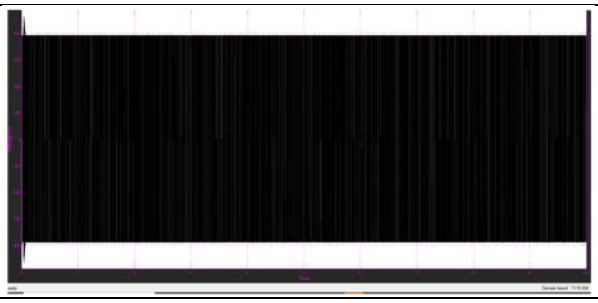

Fig. 5: Inverter output voltage

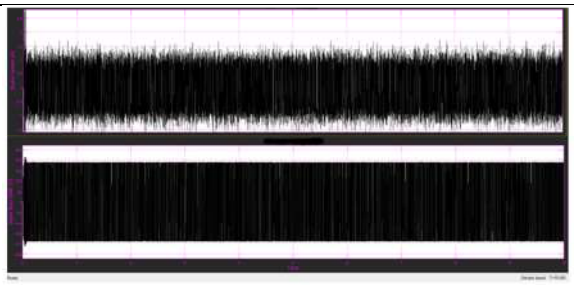

Fig. 6: Motor stator current and back EMF

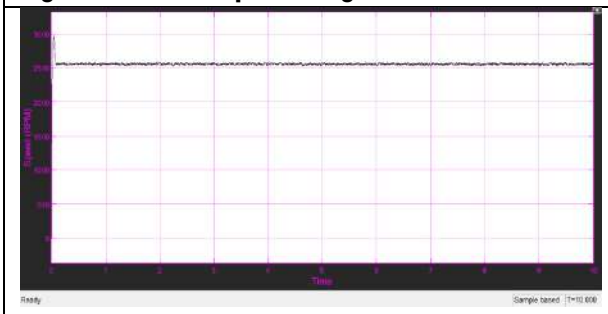

Fig. 7: Speed of the machine

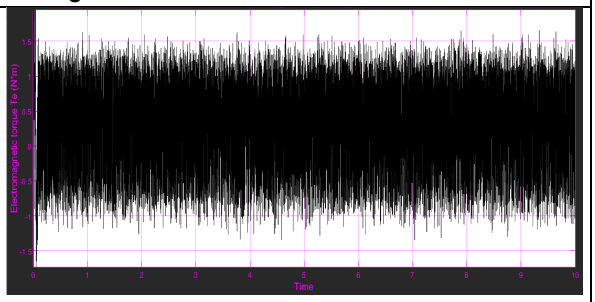

Fig. 8: Torque waveform the machine

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RESEARCH ARTICLE

Evaluation and Comparison of the Different Marketed Shampoos

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ABSTRACT

Shampoos are cosmetic products which are mainly used for the cleaning of the hair and the scalp. These formulations are mostly used in the wellness of the hair. Hair is a part of human beauty and shampoos are commonly used to remove the oil, dirt, dandruff, pollutants, and other contaminant particles that are present in the hair and scalp. In the present work three branded shampoos are evaluated for the physico chemical parameters, foaming stability, cleansing reaction, wetting time and SLS content determination by spectrophotometric method.

Keywords: Shampoos, Physicochemical properties, Spectrophotometric method and comparison.

INTRODUCTION

Shampoos are the cosmetic products used for the daily cleansing of the hair and scalp. A shampoo should not damage hair or scalp and after washing the hair and scalp. It should leave the hair soft and manageable. Shampoos can be transparent are opaque which can be formulated as aqueous solutions, emulsions, liquids, lotions, creams, pastes, gels, dry shampoos etc. all shampoo formulations contains surfactants like sodium lauryl sulfate, sodium dodecyl benzene sulfonate, sorbitol esters etc, conditioning agents like lanolin, mineral oil etc, foam builders like lauroyl mono ethanolamide etc, sequesting agents like ethanol, isopropanol, esters etc, preservatives like methyl, propyl paraben etc. The P^H of the hair is between 4.5 to 5.0 and the oil in the hair scalp is called sebum. The natural hair acidity prevents fungi and bacteria growth in the hair and scalp. It is necessary to measure the performance, quality and effectiveness. The evaluation of the shampoos comprises quality control tests for visual checking, measuring physicochemical properties like P^H, density, surface tension, foam volume and wetting ability. There is a need to study about the SLS content which is the main ingredient in most of the shampoos. Therefore the present study is aimed to evaluate marketed shampoos for physicochemical parameters and SLS content determination by spectrophotometric method.

MATERIALS AND METHODS

DOVE, CHIK and HEAD & SHOULDERS shampoos are procured from the local vendor and these three brands contain the following ingredients.

Methods

The following methods are used for the evaluation of the selected shampoos-

Physical appearance: The 3 shampoos are inspected for clarity, foam ability and fluidity.

Determination of P^H: The P^H of the 10 % shampoo solution in distilled water was determined at room temperature (25^0C) using the P^H meter.

Determination of % solids content: The % solids content is determined by the evaporation method where the empty, clean and dry evaporating dish was weighed. Then place the 4 gm of sample shampoo in the evaporating dish again the weight was taken. Then subject this evaporating dish along with the shampoo to heating on the hot plate till the liquid portion of the shampoo has evaporated. Then weigh the dried shampoo after evaporation and report as % solids content.

Rheological evaluation: The rheological evaluation of shampoo was carried by calculating the viscosity by using the Brookfield Viscometer. The temperature of the sample was kept constant during the evaluation.

Dirt dispersion: This is carried by taking a large test tube containing 10ml distilled water; add 2 drops of shampoo and 1 drop India ink. Then the test tube is shaken for 10 times. The amount of ink in the foam is measured as none, low, moderate or heavy.

Cleansing action: for this measurement 5gm of wool was wetted with grease and placed it in the 200ml of water containing 1gm of shampoo in a flask. The temperature of the distilled water is maintained at 35^0C. Then the flask was shaken for 4mins at 50rpm. The wool was removed, dried and weighed. The amount of grease removed was calculated using the following formula-

Detergency power = 100(1-T/C)

Where,

T= weight of the sebum in the test sample

C= weight of the sebum in the control sample

Surface tension measurement: This is carried by using the 10% shampoo solution in the distilled water at room temperature. For this measurement using the stalgmometer using chromic acid and purified water. The results are calculated by the following formula-

Surface tension of the shampoo= $(W_3 – W_1)\ n_1$

$(W_2 – W_1)\ n_2$ x surface tension of the distilled water

Where,

W_1 = weight of the empty beaker

W_2 = weight of the empty beaker + distilled water

W_3 = weight of the empty beaker + shampoo

n_1 = no. of drops of distilled water

n_2 = no. of drops of shampoo solution

Foaming ability and foam stability: Cylinder shake method is used for the determination of foaming ability. This is carried by taking 50ml of 1% shampoo solution placed in a 250ml graduated cylinder and covering the cylinder using hand continue by shaking for 10 times. The total volumes of the foam contents after 1 min shaking were recorded and the foam volume was calculated immediately after shaking the volume of foam at 1min intervals for 4 mins are recorded.

SLS content determination: This is determined by the spectrometric method using methylene blue as reagent and the colored solution is measured at 653nm. The standard SLS solution is prepared in the range of 10 – 50 µg/ml and sample unknown solution concentration is plotted from the calibration graph of the standard. Standard solution treated with 2ml of 2% methylene blue solution and volume is made upto 10ml with distilled water and then the solution is extracted with the chloroform. And the colored solution is measured at 653nm using the visible spectrometer.

RESULTS AND DISCUSSION

Physical appearance: The 3 shampoos are inspected for clarity, foam ability and fluidity and the results are listed in the table.2. The 3 shampoos have good characteristics with respect to foaming.

Determination of P^H: The P^H of the 10 % shampoo solution in distilled water was determined at room temperature (25^0C) using the P^H meter. The P^H of shampoo is a very important characteristic for healthy hair, irritancy of the eyes and stabilizing the ecological balance of the scalp. The current trend is a shampoo with low PH value minimizes the damage to the hair. The results are mentioned in table.3.

Determination of % solids content: It is hard to work into hair or hard to wash out if the shampoo contains too many solids. The results of % solids are tabulated in the table.4. As per results the % solid contents are within the limit.

Rheological evaluation: The rheological evaluation of shampoo was carried by calculating the viscosity by using the Brookfield Viscometer. The temperature of the sample was kept constant during the evaluation. The shampoo's rheological parameters such as viscosity of the shampoo gradually changes by increasing the rpm due to the time dependence. The results obtained showed the decrease in the viscosity with increase in the rpm. By taking this into consideration we can state that the selected shampoos are pseudoplastic in nature. The results are tabulated in table.5**.**

Dirt dispersion: This is carried by taking a large test tube containing 10ml distilled water; add 2 drops of shampoo and 1 drop India ink. Then the test tube is shaken for 10 times. The amount of ink in the foam is measured as none, low, moderate or heavy. The shampoo that concentrates the ink in the foam will be considered as poor quality and the dirt is not removed properly. The dirt which stays in the foam will be difficult to rinse away and will redeposit in the hair. The selected 3 shampoos showed the high results that are in good quality and no dirt will stay in the foam. Hence the selected 3 shampoos are satisfactory.

Cleansing action: The cleansing action results obtained are tabulated in the table.6 and are a significant difference in the amount of sebum removed by the shampoo selected. The detergency ability of the shampoos was found in between 18-33% and represents the high cleansing action as shown by the selected shampoos.

Surface tension measurement: An ideal shampoo should decrease the surface tension of the pure water to about 40 dynes/cm^2. The results found are tabulated in table.7. The detergent action of any shampoo is well explained by the surface tension reduction. The selected 3 shampoos reduced the surface tension of the water from 78 dynes/cm^2 to 31-33 dynes/cm^2 which indicate the selected shampoos showed the good detergent action.

Foaming ability and foam stability: The results obtained are tabulated in the table.8. The 3 shampoos showed similar foaming characteristics in distilled water.

SLS content determination by colorimetric method: The absorbance values of the standard SLS are tabulated in the table.9 and the unknown sample concentrations are plotted and compared with that of the standard.

CONCLUSION

The selected 3 shampoos (Dove, Chik and Head & Shoulders) are evaluated for performance and the results obtained are P^H from 5.6 – 7.3 slightly acidic to neutral in nature which will help in reduction of protein loss during combing. In the present method the quality control tests performed for the evaluation of shampoos shown the good appearance, acceptable viscosity range with pseudoplastic flow, dirt dispersion is good, acceptable surface tension range, foaming ability, foam stability and Sodium lauryl sulfate content is also within the range. Hence I conclude this research work proves that the Dove, Chik and Head & Shoulders marketed formulations are up to the quality and passed all the tests.

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Table 1: Main Ingredients of the selected shampoos

DOVE	CHIK	HEAD &SHOULDERS
Water	Water	Water
Sodium lauryl sulfate	Sodium lauryl sulfate	Sodium lauryl sulfate
Glycol distearate	Glycol distearate	Glycol distearate
Fragrance	Fragrance	Fragrance
Glycerin	Glycerin	Glycerin
Dimethicone	PEG-45	Dimethicone
Sodium sulfate	Hydroxy propyl trimonium chloride	Sodium benzoate
EDTA	EDTA	Benzyl alcohol
Titanium dioxide	Titanium dioxide	Titanium dioxide

Table 2: Physical appearance evaluation

S.No	Name of the Shampoo	Physical appearance
1.	Dove	White, good foaming
2.	Chik	Black, good foaming
3.	Head & Shoulders	White, good foaming

Table 3: P^H of the selected shampoos

S.No	Name of the Shampoo	P^H
1.	Dove	6.16
2.	Chik	5.6
3.	Head & Shoulders	7.3

Table 4: % Solids content evaluation

S.No	Name of the Shampoo	% solids
1.	Dove	22.11±0.02
2.	Chik	23.45±0.02
3.	Head & Shoulders	24.51±0.02

Table 5: Viscosities of the selected shampoos

Speed	Dove		Chik		Head & Shoulders	
rpm	%Tor	Viscosity	%Tor	Viscosity	%Tor	Viscosity
0.5	21.90	82150.3	10.13	7692.33	10.62	16533.33
1	32.98	54138.1	15.21	6934.1	11.39	14316.67
1.5	41.01	49189.2	18.18	5945.0	15.28	11427.01
2.0	44.76	46343.0	21.22	5146.21	23.39	9220.02
2.5	49.68	34829.1	24.83	4821.01	41.49	7286.62

Table 6: Cleansing Action evaluation

S.No	Name of the Shampoo	% Cleansing
1.	Dove	32.51±0.03
2.	Chik	18.91±0.09
3.	Head & Shoulders	33.51±0.02

Table 7: Surface tension evaluation

S.No	Name of the Shampoo	**Surface tension** dynes/cm^2
1.	Dove	31.37±0.62
2.	Chik	33.61±0.42
3.	Head & Shoulders	32.15±0.02

Table 8: foam ability evaluation

Time	Foam volume (mL)		
(mins)	Dove	Chik	Head & Shoulders
1	180	177	180
2	177	166	174
3	168	165	170
4	165	163	168
5	164	161	166

Table 9: absorbance of SLS

Concentration µg/ml	Absorbance
10	0.102
20	0.206
30	0.309
40	0.403
50	0.507

Table10: Absorbance of selected shampoos

Name of the shampoo	Absorbance	Concentration found µg/ml
Dove	0.060	11
Chik	0.081	12
Head & Shoulders	0.189	19

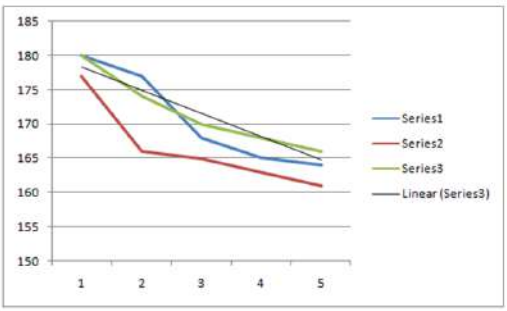

Fig 1: Foam volume evaluation
Blue line-Dove shampoo
Red line- Chik shampoo
Green line- Head and shoulders

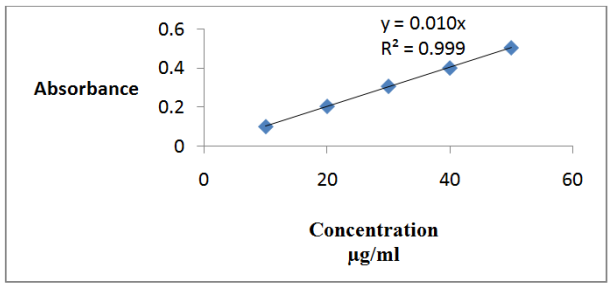

Fig 2 : calibration graph of standard SLS

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RESEARCH ARTICLE

A Study on the Challenges of Implementing HRD Practices in the Covid 19 Pandemic in it Industries in Tamilnadu

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ABSTRACT

This study finds out the challenges of implementing HRD practices in the Covid 19 pandemic in IT industries. The sample was selected from the employees of selected 25 IT firms. A structured online mailed questionnaire, was used to collect the data. The collected data were analyzed using SPSS 26 software. Descriptive statistics, reliability analysis and SEM model used for analysis. The major findings of the study reveal that HRD practices is a major influencing factor to increase employee's performance.

Key words: HRD Practices, Employee Performance, IT firms, COVID -19, TamilNadu.

INTRODUCTION

Human Resource Management is a dynamic term dealing with different people in different ways, in a different situation to carry out different results. In its simple term, HRM deals with human relationship moldings and develops human behaviour and attitude towards the job and organisational requirements. Human Resource Management is a process of managing an organisation's people with a human approach to the workforce, enabling the manager to view his people. Development of human resources is important for any organization that would like to be dynamic and growth-oriented. The human Resource Development (HRD) system aims at creating such a climate. Several HRD techniques have been developed in recent years to perform the above task based on certain principles. This unit provides an understanding of the concept of the HRD system, related mechanisms and the changing boundaries of HRD.

HRD in an organizational context is the sub-system of Human Resource Management. It is concerned with enhancing employees' knowledge, skills, aptitudes, and values and enabling them to perform the present and future jobs more effectively and efficiently. It aims to link productivity with people and a sense of personal fulfilment.

REVIEW OF LITERATURE

Emerging HR issues became notable concerns for organisations while overseeing risk management (Cooke et al. 2021; Minbaeva 2020; Verma and Gustafsson., 2020).HR practices in this covid period is critical for organisations, and must prepare a contingency plan for managing the risks associated with HR related problems (Carnevale and Hatak 2020). De Cieri and Lazarova (2020) studied the health and safety of employees in this covid period, and Adam et al. (2021) studied and focused on the issues and measures to be taken for the post-pandemic world. The modern communication technologies like machine learning, artificial intelligence, the Internet of Things, and cloud computing has aided innovation in HR practices during the pandemic (Aurelia and Momin 2020).

HRD practices are envisioned to support employees as well as organizations to achieve their work goals, whereas HRD professionals are intended to provide learning opportunities to the organizational members to nurture their expertise (Jeong and Park, 2020). The changes in the international market scenarios of human resources management have influenced the Pakistani industries to look internally for the development of human resources (Rathore et al., 2020). The Human Resource Development (HRD) concept is focused on the humanistic view (Collins, 2019) and highlights the concerns for national, societal, organizational, and individual development. Boon et al. (2018) conducted a study on integrating strategic human capital and strategic human resource management. The study further revealed that a collaboration between strategic human capital and strategic human resource management research would improve research on human capital in organizations.

Knies et al. (2018) reviewed the literature on strategic human resource management and public-sector performance: context matters. The review supplemented initial findings on strategic human resource management in the public-sector context by providing an outlet for studying HRM, employees' attitudes and behaviours, and individual and organizational performance in a public-sector context. Mierlo et al. (2018) conducted a study on the dynamic nature of HRM implementation: a structuration perspective. A comprehensive framework that assists in understanding the process of HRM implementation was developed. The results of the study suggest that various organizational factors influence HRM practices. The author further indicated that, for successful implementation, HRM practices need to become inscribed into the interpretive schemes of corporate and the allocations of resources.Behaviors of employees change with changing the environment and organizational practices (Stalin et al.,2019).

Uraon (2018) conducted a study on the impact of HRD practices on organizational commitment and intention to stay within selected software companies in India. Data were collected from 516 employees of different software companies. The study results show that HRD practices have a positive impact on employee intentions to stay and the three components of organizational commitment. The study further revealed that affective and normative commitment positively affected employee's choice to stay. Singh and Rao (2017) investigated HR practices, learning culture and human capital: a study on Indian business and professional service sector. The study results suggest that the relationship between HR practices and learning-oriented culture positively influences human organizational capital. The study further indicates that knowledge management mediated the Organization between HR practices, corporate human capital, learning-oriented culture and administrative, human capital. Nieves and Quintana (2016) examine the mediating role of human capital in the relation between human resource management practices and innovation in the hotel industry. The purpose of the study was to increase understanding of the mediating role of human capital in the relation between human resource management practices and innovation. Data was collected from 109 organizations through questionnaires.

RESEARCH METHODS

This study applied a quantitative method to explore the challenges of implementing hrd practices in the Covid 19 pandemic in it industries in Tamilnadu. The research design of the study is descriptive. Researcher uses systematic sampling design to collect the data. A list of all employees working in the selected 25 IT industries were considered as population and through on line questionnaire the data were collected from 251 respondents. The researcher used Likert's five-point scale for the questionnaire. The data collected from March 2021 to June 2021 in the second Phase of COVID period. The statistical tools used for the study are descriptive, reliability analysis, and SEM.

DATA ANALYSIS: Descriptive Analysis

A maximum of 62 percent of the employees in the study are female. The vital age group of the employees is21 to 30 years. 67.3 percent of the employees are unmarried'. The most vital educational qualifications among the employees are under graduation. The vital level of personal income per month among the employees is Rs.30, 000 – 45,000. The experience of the employees is 5 to 10 years. The hours worked per day by the employees are 8.00 to 10.00 hours in this COVID period. A structural model was developed to find out the influence of internal, external HR planning and practice, satisfaction towards HR practices on organization's performance. Amos version 21 was used to derive the model. From the above table 4.1, it is clear that all the HRD variables are having a very good reliability score (Cronbach alpha >0.70) indicates that the factors are highly significant and important to predict the HRD practices. Since P value is greater than 0.05, the null hypothesis is rejected at 5 % level of significance with respect to Overall HRD practices variables between the three group of IT organization except 'Employee engagement', 'Succession planning', 'Recruitment and selection', 'Organizational culture', 'Digital transformation' and 'Work from home'. From the table 4.2, P value is less than 0.05, the null hypothesis is rejected at **5% level** of significance.

Friedman test indicates a significant difference between mean rank of Employee performance that employees working in IT Companies in Tamilnadu. 'Digital transformation' (Mean rank- 11.07), 'Reward system' (Mean rank- 10.66), 'Employee Competencies' (Mean rank- 10.17) variables are rated high by the IT employees. These are followed by the least mean rank of HRD practices such as 'Organizational culture' (Mean rank- 5.79), 'Recruitment and selection' (Mean rank- 5.45), 'Work from home' (Mean rank- 4.84) rated low by the respondents. The Chi-square value 3084.388 is significant at 5 percent level. Hence concluded that there is a significant difference between mean ranks towards various HRD practices variables rated by the employees working in various IT Companies in Tamilnadu.

From the model, the coefficient of Human resource development practices is .587 represents the partial effect of employee engagement, holding the other variables as constant. The estimated positive sign implied that such effect is positive that employee engagement would increase by .587 for every unit increase in Human resource development practices and the coefficient value is significant at 1% level.A structural model (Figure -1) was developed to find out the influence of HRD practice, Challenges towards the implementation of towards HRD practices and commitment towards employees' performance. Amos version 21 was used to derive the model.

From the structural model 4.1,the coefficient of Human resource development practices is 0.470 represents the partial effect of organizational commitment, holding the other variables as constant. The estimated positive sign implied that such effect is positive that organizational commitment would increase by 0.470 for every unit increase in Human resource development practices and the coefficient value is significant at 1% level. A structural model (Figure -1) was developed to find out the influence of HRD practice, Challenges towards the implementation of towards HRD practices and commitment towards employees' performance. Amos version 21 was used to derive the model.

From the model, the coefficient of Human resource development practices is .289 represents the partial effect of employee competencies, holding the other variables as constant. The estimated positive sign implied that such effect is positive that employee competencies would increase by .289 for every unit increase in Human resource development practices and the coefficient value is significant at 1% level.

From the model, the coefficient of Human resource development practices is 0.509 represents the partial effect of training and development, holding the other variables as constant. The estimated positive sign implied that such effect is positive that training and development would increase by 0.509 for every unit increase in Human resource development practices and the coefficient value is significant at 1% level.

From the model, the coefficient of Human resource development practices is .304 represents the partial effect of succession planning, holding the other variables as constant. The estimated positive sign implied that such effect is positive that succession planning would increase by .304 for every unit increase in Human resource development practices and the coefficient value is significant at 1% level.

From the model, the coefficient of Human resource development practices is 0.320 represents the partial effect of performance appraisal, holding the other variables as constant. The estimated positive sign implied that such effect is positive that performance appraisal would increase by 0.320 for every unit increase in Human resource development practices and the coefficient value is significant at 1% level.

From the model, the coefficient of Human resource development practices is 0.295 represents the partial effect of career development, holding the other variables as constant. The estimated positive sign implied that such effect is positive that career development would increase by 0.295 for every unit increase in Human resource development practices and the coefficient value is significant at 1% level.

From the model, the coefficient of Human resource development practices is -.552 represents the partial effect of reward system, holding the other variables as constant. The estimated negative sign implied that such effect is negative that reward system would decrease by -.552 for every unit increase in Human resource development practices and the coefficient value is significant at 1% level.

From the model, the coefficient of Human resource development practices is 0.437 represents the partial effect of recruitment and selection, holding the other variables as constant. The estimated positive sign implied that such effect is positive that recruitment and selection would increase by 0.437 for every unit increase in Human resource development practices and the coefficient value is significant at 1% level.

From the model, the coefficient of Human resource development practices is 0.033 represents the partial effect of Organizational culture, holding the other variables as constant. The estimated positive sign implied that such effect is positive that Organizational culture would increase by 0.033 for every unit increase in Human resource development practices and the coefficient value is insignificant at 1% level.

From the model, the coefficient of implementation challenges is 0.190 represents the partial effect of Human resource development practices, holding the other variables as constant. The estimated positive sign implied that such effect is positive that Human resource development practices would increase by 0.190 for every unit increase in implementation challenges and the coefficient value is significant at 1% level.

From the model, the coefficient of implementation challenges is 0.125 represents the partial effect of Digital transformation, holding the other variables as constant. The estimated positive sign implied that such effect is positive that Digital transformation would increase by 0.125 for every unit increase in implementation challenges and the coefficient value is significant at 1% level.

From the model, the coefficient of Human resource development practices is 0.264 represents the partial effect of Digital transformation, holding the other variables as constant. The estimated positive sign implied that such effect is positive that Digital transformation would increase by 0.264 for every unit increase in Human resource development practices and the coefficient value is significant at 1% level.

From the model, the coefficient of Human resource development practices is 0.928 represents the partial effect of Work from home, holding the other variables as constant. The estimated positive sign implied that such effect is positive that Work from home would increase by 0.928 for every unit increase in Human resource development practices and the coefficient value is significant at 1% level.

From the model, the coefficient of Digital transformation practices is 0.128 represents the partial effect of Work from home, holding the other variables as constant. The estimated positive sign implied that such effect is positive that Work from home would increase by 0.128 for every unit increase in Digital transformation and the coefficient value is significant at 1% level.

From the model, the coefficient of Digital transformation is 0.099 represents the partial effect of employees' performance, holding the other variables as constant. The estimated positive sign implied that such effect is positive that employees' performance would increase by 0.099 for every unit increase in Digital transformation and the coefficient value is insignificant at 1% level.

From the model, the coefficient of Work from home is -.074 represents the partial effect of employees' performance, holding the other variables as constant. The estimated negative sign implied that such effect is negative that employees' performance would decrease by -.074 for every unit increase in Work from home and the coefficient value is insignificant at 1% level.

From the model, the coefficient of Human resource development practices is -0.165 represents the partial effect of employees' performance, holding the other variables as constant. The estimated negative sign implied that such effect is negative that employees' performance would decrease by -0.165 for every unit increase in Human resource development practices and the coefficient value is insignificant at 1% level.

CONCLUSION

The study of HRD variables will contribute to the improvement of employee welfare of IT industries in Tamilnadu. An understanding and identification of critical variables in the practices of HR and their association with employees'(organisational) performance is provided; these may motivate employees into positive direction and increase work efficiency. In the current Covid situation, crises are inevitable. However, no one can predict a crisis with the magnitude of COVID-19, which has accelerated the disruption of traditional methods of HRM. It created challenges for managers and HRM practitioners, who were not equipped with information, resources, and competencies to fight this pandemic. Besides these challenges, COVID-19 has opened the door to opportunities for organizations to direct their future actions in HRM. The insights provided in this paper into the future directions in HRM should help them to develop an intervention plan adapted to the needs of their organizations and employees.

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Table1. HRD practices variables

S.No	HRD practices variables	'F' statistics	Cronbach alpha
1	Employee engagement	1.6941	0.7851
2	Organizational Commitment	3.1664*	0.8074
3	Employee Competencies	5.0319*	0.8338
4	Training and Development	3.4927*	0.9015
5	Succession planning	1.8952	0.7931
6	Performance appraisal	3.6509*	0.7748
7	Career development	3.6418*	0.8975
8	Reward system	5.8158*	0.8044
9	Recruitment and selection	2.2514	0.7946
10	Organizational culture	1.5833	0.8158
11	Digital transformation	1.0417	0.8706
12	Work from home	0.8374	0.8218

Table 2 Friedman test for significant difference between mean ranks towards various HRD practices variables.

S.No	HRD practices	Mean Rank	Chi-square value	'P' value
1	Digital transformation	11.07	3084.388	<0.05*
2	Reward system	10.66		
3	Employee Competencies	10.17		
4	Succession planning	9.84		
5	Training and Development	9.32		
6	Career development	8.47		
7	Organizational Commitment	7.29		
8	Employee engagement	6.89		
9	Performance appraisal	6.41		
10	Organizational culture	5.79		
11	Recruitment and selection	5.45		
12	Work from home	4.84		

* Denotes significant at 5% level

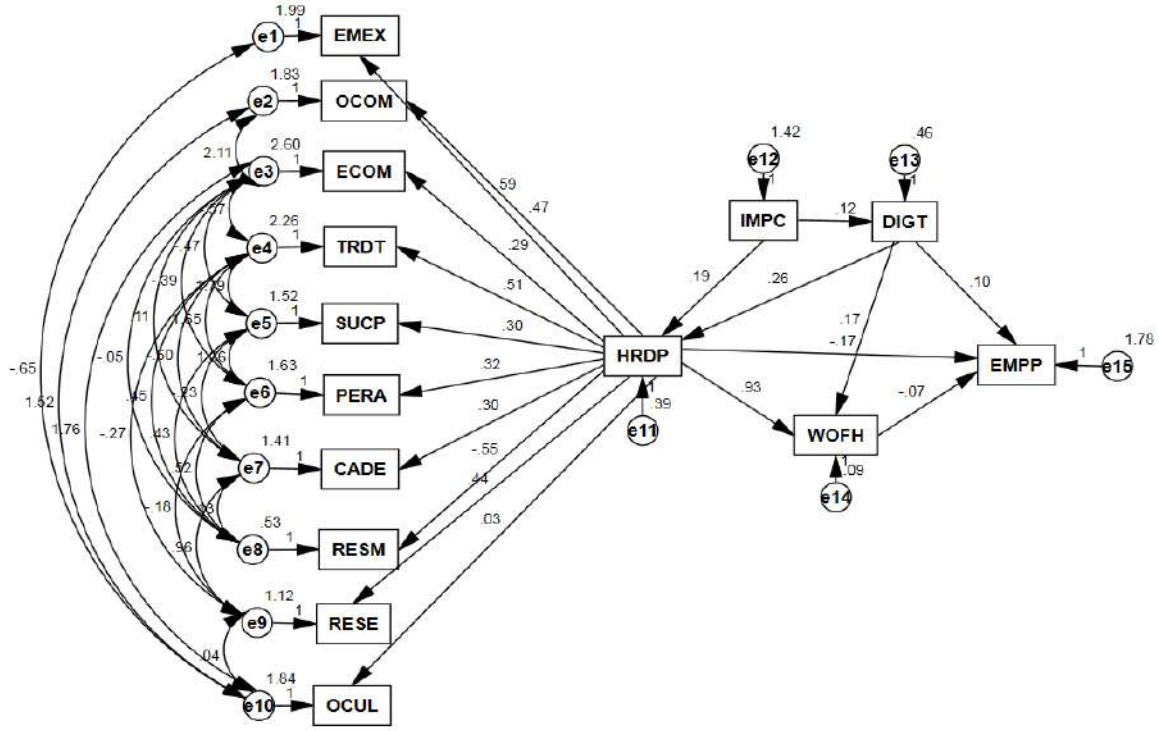

Figure. 1. Structural model

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RESEARCH ARTICLE

A Study on Effect of Modern Day to Day Technology on Human Lifestyle

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ABSTRACT

Modern living impacts us in many ways, destroying of moral values, Health aspects, physical, mental, moral developments, environment and cultural values and also restructuring business, thinking process with life style. In my views, people are becoming more Technologically advanced but some disadvantages that are because of ,pollution is increasing adversely, global warming, people are suffering from a lots of diseases, especially are respiratory diseases, heart diseases, skin diseases or cancer etc. There is Increase high-level of stresses in daily life living. Mobile phone cause harm to human brain activity. Researchers found that human brain is sensitive to the magnetic field of the phones antenna. They found that the brain activity was affected after the use of mobile phone. And although there are clear and calculated implications that this may have for health, study shows definitively that exposure to electromagnetic radiation emitted by mobile phones have direct and measurable effect on the brain. So from this study we can come to a conclusion that, modern living, modernisation , westnigation, and high technological development has made the people of our country unhealthy, weak destroying of moral values and disease prone. In this study try to highlights the recent facts with research analysis of the technology on human health and life, also try to present mental or physical health aspects.

Keywords: Modernisation Bisophenol A (BPA), Radiation, Abnormalities, Heart Disease and Materialistic.

INTRODUCTION

Modern living and technologies influence us in many ways; these are both advantages and disadvantages. Advantages are modern life ,people are becoming more technologically advanced and they can come to know about many things which they didn't know before advancement some disadvantages are there because of pollution ,global warming, people are suffering from a lot of diseases such as –heart disease, high cholesterol, brain cancer ,asthma,

allergy etc. The present day generation like buying vehicles, the vehicles pollute the air and are dangerous for the environment and human health. Exhaust fumes contain dangerous molecules that threaten human health ,such as carbon monoxide ,which impairs oxygen flow to the brain, and sulphur oxides ,which can cause respiratory illnesses ,The increase global warming produces nitrogen oxide, which can cause acid rain ,and ozone also increase noise pollution ,air pollution, or worsen other existing conditions causing chest congestion and brevities. Next to emphasis is consumption of drugs, alcoholic beverages ,celebrations, eating more fast food in open garden ,hotels are also prevalent in modern living ,reducing health awareness and sociocultural values of Indians. The National Institute of health in the United States keep dictating that the mobile phones, plastic bottles, computer use amplified brain activity is more than earlier investigated, reason remains the various innovations in the technology driven world. India is a land of various cultures, traditions, religious and art, live together. Indian society is considered as one of the most cultured in the world. Impacts of westernisation can be seen in the changing life styles of Indians. Well, this is no harm in adopting lifestyles from other culture but forgetting our own moral values is something wrong and could have a negative impact in the long run. When the people of the society get enhance and advanced in all aspects like education ,relationship, attitude ,thinking ,clothing, food, media, fashion, everything seem to have got affected by the advent of western culture. West irrigation has promoted the single families .marriages is breaking up at a fast rate. Even the teenager's tent to have pre marital sex, they believe to choose their own life partners rather going with parent's choice. Modern living has mainly affected physical, mental, moral environmental and health aspects. In the year 2009-2010 when we randomly surveyed on fifty families, of Gujarat and Madhya - Pradesh. On the effects of five aspects ,physical ,mental, moral, environmental and health aspects the result found were shocking which proved the effects of modernisation and westernisation increase which dominate ,the different negative effects on different life aspects of Indian families.

Physical	Mental	Moral	Environmental	Healthiness
40%	78%	98%	60%	80%

The study will be presented – American Heart Association scientific session 2016 in Chicago-

The majority of people who adopted healthy lifestyles behaviours in young adulthood maintained a low cardiovascular risk profile in middle age .cardiovascular risk health is due primarily to lifestyle factors (modernisation ,westernisation ,technological)and healthy behaviour, not heredity. The five healthy lifestyles ignore Indian people not smoking an alcohol intake, weight control, physical activity and a healthy diet, by the age of as low as 25-30 years. Due to the modernisation there are different types of advanced medicines, and treatments develop for pregnancy test and saves many foetus from the hands of death, but some time in this stage the unborn baby faces many threats from the radiation received by the mother during pregnancy, in most cases foetuses exposed to excessive radiation tend to be born with abnormities .So, from this study we can come to conclusion that technological development impacts on human healthy life. In Washington, one research study calculated that plastic bottles and polybags are very harmful for human health, but modern living people used to for, Bisopenol A the primary chemical used to produced hard plastics like bottles, politeness can be a potential risk factor for metabolic syndrome, A new research from the university of Cincinnati (UC) using fresh human fat tissues in their study .the UC team found that BPA suppresses a key hormone, adiponectin. Adiponacting is responsible for regulating insulin sensitively in the body and puts people at a substantially higher risk for metabolic syndrome .According to estimates, over 80% of people tested have measurable BPA in their bloodstream.

Major factors of BPA on human health

- Increase testosterone level in men.
- Reduce sense quality.
- Increase heart disease, asthma, and diabetes risk.
- Worsening male sexual functions.
- Harm testis function in adulthood.
- Cause male impotency.

- Fertility problems in female raise breast cancer.
- Damage egg quality in woman.

The National Institute of Health in the United States, Keep dictating that the, mobile phone us amplified brain activity than earlier investigated, Reason remains the various innovations in the technology drive world .the study by the institute has it that a considerable amount of sugar level rises in the brain thus increasing the brain activities when phone calls are powered on and used by cell phone users for several minutes of call made .Various study indicate that the emission from a cell phone can be extremely harmful and cause genetic damage ,Increased brain cancer and metabolic disorder . In addition, although these are clear and concluded implications that this may have for health, Study shows definitively that exposure to electromagnetic radiation (in the fome of microwaves) emitted by mobile phones have direct and measurable effect on the brain. The study conducted in 2014-15 on the disadvantages of mobile phones prone that it causes maximum mental stress in about 80% of people, leads to family complications up to 72%and is the main reason of about 64%of accidents. Head or upper body pain or disability find out students for participating in the survey and collected the survey results for detailed analysis. Based on the results, 27.5% of them were known to be unaffected by pain symptom, 44.5% of them were affected by hade ache pain, for moderate hand or hand; there were 27% of them. Therefore, by all this avoidances shows modernisation, westernisation, and technological developments impacts on human health and daily living life made complicated, and unhealthy.

Family complication	Mental stress	Accidents
72%	80%	64%

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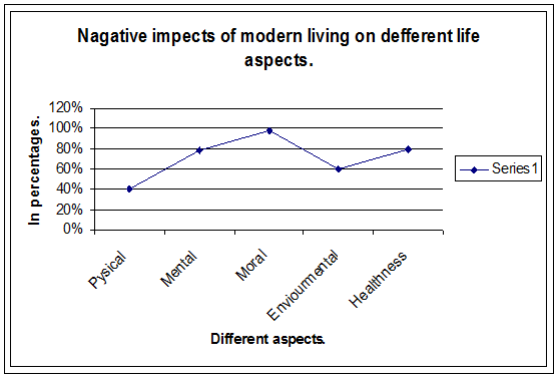

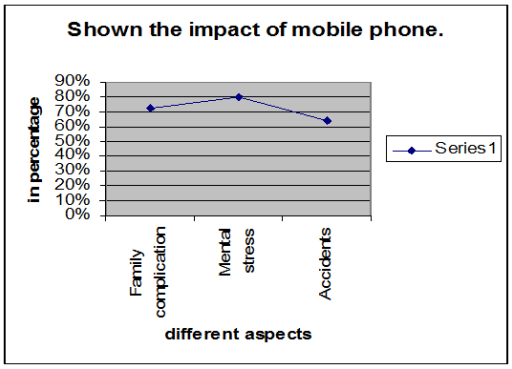

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REVIEW ARTICLE

Effects of Respiratory Muscle Exercise in Patients with Chronic Obstructive Pulmonary Disease: A Narrative Review

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ABSTRACT

The aim of this narrative review is to examine the available literature to evaluate whether respiratory muscle exercise is effective in patients with chronic obstructive pulmonary disease. A computer-based literature search was done using the Pubmed, Pubmed Central, Science Direct and Google Scholar. Relevant articles with full text published in English till 2021 were screened and included. Editorials, Commentaries, Discussion papers, Conference abstracts, Reviews and Duplicates were excluded. We included only studies with full text articles. After screening all the articles, 10 relevant articles were included in the review.

Keywords: Respiratory muscle exercise, Breathing exercise, IMT, COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease characterized by airflow limitation and small airways, which is an irreversible process [1]. According to a report by the World Health Organization (WHO), there are 80 million people with COPD worldwide [2] and more than 6.3% of the population over 30 years in the Asia-Pacific countries suffer from this condition, which ranges from moderate to severe [3]. Effective management of this troublesome symptom, and the associated poor health status, represents a major challenge for caregivers. Chronic breathlessness, reduced exercise capacity and habitual physical inactivity are inexorably linked and are strong predictors of reduced survival in COPD [4-6]. Dyspnea is an important and debilitating symptom in patients with

chronic obstructive pulmonary disease (COPD) [7]. Several pathophysiological factors known to contribute to dyspnea include: 1) increased intrinsic mechanical loading of the inspiratory muscles; 2) increased mechanical restriction of the chest wall; 3) functional inspiratory muscle weakness; 4) increased Ventilatory demand related to capacity; 5) gas exchange abnormalities; 6) dynamic airway compression; or 7) cardiovascular effects [8].

Breathing technique is an all embracing term for a range of techniques such as active expiration, slow and deep breathing, pursed lips breathing, relaxation therapy, body positions such as forward leaning, inspiratory and expiratory muscle training and diaphragmatic breathing. The aims of these techniques vary considerably and include the improvement of (regional) ventilation and gas exchange, reduction of dynamic hyperinflation, improvement of respiratory muscle function, reduction in dyspnea and improvement of exercise tolerance and quality of life. In patients with COPD, breathing techniques aim at relieving dyspnea by: 1) increasing strength and endurance of the respiratory muscles; 2) optimizing the pattern of thoraco-abdominal motion; and 3) reducing dynamic hyperinflation of the rib cage and improving gas exchange [9]. In patients with COPD, Controlled breathing is used to relieve dyspnea by 1) Reducing dynamic hyperinflation of the rib cage and improving gas exchange, 2) Increasing strength and endurance of the respiratory muscles, 3) Optimizing the pattern of thoraco-abdominal motion. In addition, psychological effects (such as controlling respiration) might also contribute to the effectiveness of controlled breathing [10].

Reduced endurance and strength of the inspiratory muscles are frequently observed in chronic lung disease and contribute to dyspnea sensation. Breathing techniques and body positions aim to improve the length-tension relationship or geometry of the respiratory muscles (in particular of the diaphragm) or increase strength and endurance of the inspiratory muscles. According to the length-tension relationship, the output of the muscle increases when operating at a greater length, for the same neural input. At the same time the efficacy of the contraction in moving the rib cage might improve. Also, the piston-like movement of the diaphragm increases and thus enhances lung volume changes. In contrast to what is often believed, diaphragm displacement and its contribution to tidal volume during resting breathing have not been shown to be different in COPD patients. During increased levels of ventilation, the contribution of the diaphragm is reduced in more severe COPD. The diaphragm can be lengthened by increasing abdominal pressure during active expiration or by adopting body positions such as forward leaning. Specific training of the respiratory muscles might enhance their strength and/or endurance capacity and thus Ventilatory capacity, relieve symptoms and improve exercise performance [9, 11-13].

Ventilatory Muscle Training (VMT) is an important component of the physical rehabilitation which improves the strength and endurance of the respiratory muscles. The different types of Ventilatory muscle training includes Incentive Spirometry, inspiratory resistance training with various Resistive Inspiratory Devices, and different breathing techniques for the relief of dyspnoea [14]. Incentive Spirometry and Resistive Inspiratory Devices are widely used to improve inspiratory muscle strength and to reduce dyspnea. These devices offer resistance while performing inspiration. Incentive Spirometer is a simple instrument which provides visual and auditory feed-back to the patient while performing inspiration, so that patient can achieve their preset goals. It encourages deep breathing and a sustained inspiration [15]. In this study, we performed a review on the effect of respiratory muscle exercise (Breathing exercise, incentive spirometry, IMT) in patient with chronic obstructive pulmonary disease.

METHODOLOGY

A search of the available literature was performed to evaluate the effect of respiratory muscle exercise. The population of interest were all patient chronic obstructive pulmonary disease. The intervention studies were breathing exercise, incentive spirometry, IMT to regular care with medication (no training programme). Pubmed, Pubmed central, Science direct and Google scholar were searched from the earliest date available within each data base up to 2021.

Searching strategy: Total 254 articles were identified from computer based literature search. After excluding the duplicates, interventional studies, editorials, commentaries, discussion papers, conference abstracts, reviews and abstracts 78 full text articles were screened. Out of that, only 11 articles were included as matched with the aim of this review.

Effect of Breathing Exercise in Patients with Chronic Obstructive Pulmonary Disease

Diaphragm is an important muscle that help your breath. Diaphragmatic breathing is a type of breathing exercise that helps strength the diaphragm. A 29 patient with moderate and severe COPD were chosen. They were monitored using respiratory inductance plethysmography and metabolic gas analysis. In this the subjects did 4 min of natural breathing, followed by 2 minutes of DB and then again 4 minutes of natural breathing. The results showed that diaphragmatic breathing is effective in increasing diaphragmatic mobility, increase inspiratory muscle strength and lower score of dyspnea and hypoxia. Also in patients with COPD, DB can improve breathing pattern and Ventilatory efficiency without causing dyspnea [16]. Mendes *et. al.* performed a study to assess the effects of diaphragmatic breathing and diaphragmatic breathing combined with pursed-lips on chest wall kinematics, breathlessness, and chest wall asynchrony in subjects with COPD, the study was also performed to assess whether the combination of both exercises reduces the adverse effects of diaphragmatic breathing while maintaining its benefits. Results show that there was an increase in the asynchrony, both breathing exercise were able to improve chest wall volumes without effect of dyspnea [17].

Multiple physiological process in the body are regulated by autonomic nervous system (ANS). Physiological process such as adjusting heart rate, blood pressure, gastrointestinal secretion, temperature regulation are monitored by ANS. It is also responsible for vagally mediated reflex constriction of airway smooth muscle, secretion from submucosal glands, capillary permeability and blood flow in the bronchial circulation, cardiovascular responses to exercise. Dysfunction of the ANS is recognized by the symptoms that result from the failure of sympathetic or parasympathetic components. A study conducted to investigate whether there is sympathetic activation in COPD patients in the absence of hypoxia and whether slow breathing has an impact on sympathoexcitation and baroreflex sensitivity. Efferent muscle sympathetic nerve activity, blood pressure, cardiac frequency and respiratory movements were continuously measured in 15 COPD patients and 15 healthy control subjects. Baroreflex sensitivity was analyzed by autoregressive spectral analysis and the alpha-angle method. Result shows, sympathovagal imbalance is present in normoxic chronic obstructive pulmonary disease patients. The possibility of modifying these changes by slow breathing may help to better understand and influence this systemic disease [18].

Pilates breathing is defined as a uses a normal breath in (not a deep breath in) and directs the breath into the sides of the ribs (rather than the lower belly) in order to maintain abdominal activation. A study was conducted to compare Ventilatory parameters during DB and PB in COPD patients and healthy adults. Two groups each of Fifteen COPD patients (COPD group) and fifteen healthy patients (healthy group) performed three types of respiration: natural breathing (NB), DB, and PB, the respiration pattern was being analyzed by respiratory inductive plethysmography. Evaluation was also done on parameters of time, volume and thoraco-abdominal co-ordination. Positive effect such as increase in lung volume, respiratory motion and SpO2, reduction in respiratory rate was seen in DB. PB showed no changes in volume and time measurements during COPD, this breathing pattern increase volume in healthy subjects and increase oxygenation in both groups [19].

Breathing frequency is increased by physiological arousal. In COPD patients, anxiety causes hyperventilation. This results in increase in shortness of breath by causing bronchoconstriction and lung hyperinflation. Hyperinflation increase the work and effort of breathing and reduce inspiratory reserve capacity. Exercise such as active expiration, slow and deep breathing, relaxation therapy, specific body position, inspiratory muscle training and DB compresses a term "controlled breathing". 20Valenza *et al.* performed a study to assess Effectiveness of Controlled Breathing Techniques on Anxiety and Depression in Hospitalized Patients with COPD. Baseline and post intervention dyspnea, anxiety and depression, maximum inspiratory and expiratory pressure, hand grip strength and sleep quality were

measured. Quality of life was also measured with St. George's respiratory Questionnaire and the European Quality of Life questionnaire. It was concluded that measured variables improved in the intervention group. It was seen that controlled breathing exercise improve anxiety and depression in COPD patient who were hospitalized. It was also seen that control group had poorer values in all the variable after the hospitalization [21].

Effect of Inspiratory Muscle Training and Incentive Spirometry in Patients with Chronic Obstructive Pulmonary Disease

Respiratory Muscle Training (RMT) can be defined as a technique that aims to improve the strength and function of the respiratory muscles through specific exercises device. A study conducted to evaluating the effects of a specific inspiratory muscle training protocol on the structure of inspiratory muscles in patients with chronic obstructive pulmonary disease. The use of threshold inspiratory device was done. It was performed 30 minutes per day, five times a week, for 5 consecutive weeks. The inspiratory loading equivalent to 40 to 50 % of their maximal inspiratory pressure was given to the inspiratory training group. It was concluded that there was a increase in both strength and endurance of the inspiratory muscle in the inspiratory training group [22]. Maryam Bakhshandeh Bavarsad *et.al.* conducted a study on Thirty patients (27 males, 3 females) with mild to very severe COPD. They were randomly assigned to 2 groups that is training group (group T) or to a control group (group C). Patients in group T received training for 8 weeks (15 min/day for 6 days/week) with flow-volumetric inspiratory exerciser. Each patient was assessed before and after 8 weeks of training for the following clinical parameters: exercise capacity by 6-min walking test (6MWT), exertional dyspnea by Borg scale, and pulmonary lung function by spirometry. Results showed that at the end of training there was a significant increase in 6MWT, dyspnea was decrease in training group but not in control group. No changes were seen in measure of pulmonary function in both groups. Over all the value for exercise capacity and dyspnea improved after 8 weeks in group T in compare with group C [23].

Incentive spirometry device is used to facilitate a sustained slow deep breath. It is designed to mimic natural sighing by encouraging patients to take slow, deep breaths. Incentive spirometry devices which provide visual cues to the patients that the desired flow or volume has been achieved. A study was conducted to evaluate the effects of IS on pulmonary function tests, arterial blood gases, dyspnoea and health-related quality of life, study was conducted on patients hospitalized for COPD. The Result shows The use of IS appears to improve arterial blood gases and health-related quality of life in patients with COPD exacerbations.24 another study conducted with aim to compare the efficacy of Incentive Spirometry and Resistive Inspiratory Devices on Ventilatory muscle strength in COPD patients with mild to moderate dyspnea. concluded that there is no significant difference between the 2 groups. Both the interventions (Incentive Spirometer and Resistive Inspiratory Device) are equally effective, both in improving Ventilatory muscle strength and reducing the perception of dyspnea in COPD patients with mild to moderate dyspnea [25]. Hosseini *et.al.* did study to compare the effect of resistive inspiratory muscle training and incentive spirometry on respiratory pattern of COPD patients. 30 patients with moderate COPD were randomly divided into the RIMT and the IS treatment group. They concluded statistically superior performance of resistive training in improving the maximal voluntary ventilation and maximal inspiratory pressure, the difference between its results and the results of incentive spirometry is not clinically important, therefore positive clinical outcomes of incentive spirometry are sufficiently significant to encourage its use in COPD rehabilitation programs [26].

CONCLUSION

According to these articles Inspiratory Muscle Techniques (IMT), Incentive spirometry and different types of breathing exercise – These physiotherapy treatments are effective to improve exercise capacity. (6-MWT), pulmonary function, respiratory muscle strength, SpO2, Rate of Perceived Exertion. So, recommended in patient with COPD. However, all types of breathing exercise and respiratory muscle training do not significantly improve conditioning

in patient with COPD. Since the effects of BEs exercise vary significantly between types of BE and type of respiratory muscle training as well as outcome measures, care must be practiced when selecting BEs and treatment method for respiratory muscle training to ensure its effectiveness specific to COPD patients

CONFLICT OF INTEREST

None

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None

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RESEARCH ARTICLE

Study of Humanistic Approach: An Effective Teaching Strategy for Second Language Acquisition

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ABSTRACT

Learning of the second language is an indispensable part of the curriculum. As the second language is not the mother tongue of the learner, one has to stimulate the interest of the students for the learning of the second language. Thus, teaching the second language is a challenging role for the teachers. The teachers make the use of various linguistic and psychological theories to facilitate the acquisition of the second language. The learners and their learning play the centre role in the class. The teaching -learning strategies are created and developed on the basis of the need of the learners and their interest. The involvement of the student leads to the higher level of motivation that results into the real learning and the development of the competencies. The American psychologist Carl Rogers in the 1980s, laid stress on the facilitative learning. According to him, the facilitative learning is a humanistic approach to learning. This research paper will examine the characteristics of the humanistic approach of teaching and its impact on the teaching and learning of the language. The qualitative descriptive approach of the research explores the various strategies in order to find out the best practice of the learning through this approach. The paper reveals that the humanistic approach facilitates the learning and leads to the achievement of the goal by the learners. The students do not feel dominated by the mentor or the teaching strategy and the curriculum. The teacher plays the role of an ignite to develop the motivation among the students to learn through the various innovative practices. Thus, the teacher must adopt the humanistic approach while implementing the various teaching strategies in order to make the teaching -learning more effective.

Keywords: Teaching, Humanism, Effective, Strategies, Learning, Need, Self-actualisation

INTRODUCTION

The teaching and learning strategies are always in the process of evolution in order to make it more effective than the past years. As a result, various innovative practices of teaching have been discovered and implemented like visual teaching, project-based teaching, technology-based teaching, inquiry-based learning, traditional book-based teaching and so on. But each teaching strategy has its own advantages and disadvantages. One cannot name any teaching strategy as an ideal teaching strategy. If one teaching strategy has worked effectively on one group of the students, the other group of students is not behind with the other teaching strategy. Even today the traditional pattern of teaching works with the students. Thus, the teacher uses various strategies of teaching-learning to facilitate the learning by the students themselves**.** At the end of 1970's, the theorists Erickson, Roger, and Maslow proposed the humanistic approach for the second language teaching and learning. The traditional teaching method of second language focuses on the completion of the course following the summative evaluation of the performance of the student. This certification was the proof of the success and knowledge of the student in the second language but not for the overall development of the student. The earlier theories of learning and teaching which emphasize differently on the behaviour, mental and physical development, pave the way for the new approach of teaching and learning of the second language. This new approach that focuses on the development of the learner with his emotions, feelings, ideas, thoughts and the interpersonal relations is named as Humanistic Approach. According to this new approach of teaching and learning, the empathy plays a pivotal role for making the teaching and learning more effective. The Humanistic approach promotes the development of the learner as a human being. Humanistic approach of education gives importance to the students and their self-realization. The insertion of innovative practices by the teachers depends on the requirement or need of their students to make their teaching -learning more effective and humanistic. Today the availability of various pedagogical resources has increased the level of innovative practices of teaching to facilitate the learning process. The students are interested to learn and take the initiative of learning unlike the traditional approach of being forced by the teacher. The learner centric approach motivates the learner to play an active role in the classroom. This paper focuses on the characteristics of the Humanistic approach in language learning and teaching. It will also explore methods employed by the teachers for the complete involvement of the students and their active participation.

Literature Review

The Humanistic approach of teaching has evolved through various methods since 1970. They are:

- The Total Physical Response
- Suggestopedia
- The Nature Approach
- Communicative Language Teaching

The above methods emphasise only on the communication skill and the learning of the language as per the restricted curriculum. Thus, this research paper focuses on the principles of Humanistic Education that gives importance to the self-actualisation of the learner while respecting the need and freedom of the learner. The objective and purpose of the study is to employ the strategy that can develop the motivation of the students and assist them to attain their goals and in their overall development thus supporting in the bringing up of the humanistic society.

METHODOLOGY

The qualitative descriptive methodology is applied to explore the holistic approach of the humanistic method of teaching the second language.

Effective teaching-learning through Humanistic Approach

In this paper, the humanistic strategy of education has been studied through the qualitative descriptive and explorative approach that define the conditions of the learning and teaching of the language in the pragmatic manner. The Learning theory of Humanism came into existence in 1960. Abraham Maslow and Carl Rogers are the

famous psychologist who have proposed the humanistic approach in psychology. The theory emphasises on the freedom and the potential of the student. According to the theory, the human beings are all good and have the potential for their personal growth and development. Thus, the theory encourages the student for self-learning by providing them the comfortable environment. The acquisition of the language is the foremost component of the teaching and learning of the second language in the language class. One needs to develop the four skills of learning the language namely, listening, reading, writing, and speaking. These four skills can be achieved effectively when the student work together with the other learners of the class irrespective of the difference between them. As we know that learning of the language is not possible all alone, so it requires the sharing of the emotions, feelings and communication with others in the target language and in different situations of life. Thus, the humanistic approach concentrates on the development of the empathy and positive attitude to facilitate the learning and teaching of the second language. The learner of the second language learns to accept the social and cultural behaviour of the people of target language. Thus, the humanistic approach of teaching contributes to the development of the learners of the second language.

"According to Gage and Berliner (1991, cited in Aloni, 2007) the humanistic psychology can be categorised into three main principles namely 'individual self-worth', feelings are as important as facts', and 'personal, social and moral development becomes at least as important as academic development"[1]. Since two decades, the humanistic approach is the contemporary theory of teaching and learning of second language where the social identity plays an important role. The linguistic and pragmatic competences with the sociocultural interaction are the basic components of learning and teaching the second language. Thus, the social interaction provides an environment to develop the language in various situations. Dornyei, (2009, p.227) considers that "the acquiring of a language cannot be separated from the social context in which it takes place"[2]. Thus, the communicative skill is the foremost skill that fosters with the language learning in the real-life situations. The interactive activities created by the teachers enrich the linguistic competence of the student in the target language. The social environment of the communication develops the relationship between the students. Moreover, the Humanistic approach of learning enhances cognitive competence with focus on the emotions and feelings of the learner. As the needs of the learner is given an importance, the teacher concentrates on the framing of the pedagogical materials as per the requirement of the student and the curriculum.

The pandemic conditions of today's world bring forth the unprecedented challenges for the teachers as well as learners. It is essential that each one take care of the human values without any discrimination. Various teaching strategies have been evolved to make the teaching and learning of the language successful but humanistic approach of the teaching is most adaptable in the current scenario as it is most pragmatic and empathetic. It makes the learner self-dependant, confident and responsible. Each learner has the potential. Only one has to stimulate that potential. The humanistic theory develops a true learner with the self–initiated learning. "The Humanistic approach emphasises the student personal freedom, their choices, motivation, self-determination and personal goals" (Woolfolk, 2008)[3]. The personal involvement of the student for learning and his freedom of choice are initiated and practised under this theory.

The theory is influenced by experiences of a person, and it considers the person as a whole. The function of the theory is to motivate the learner to know and to learn. It develops the autonomy, and they are self-directed for the problem-solving assignments. The learning depends on the prior experience. During the teaching of the foreign language or the second language, the teachers apply the best interactive methods of teaching to motivate and to facilitate the learning of the foreign language. Teachers are the sources who stimulates the academic needs of the learner that in turn motivates the learner to move forward on their own. The teachers play the role of the facilitators. The teachers show the path to the students by demonstrating the various aspects of learning so that they could make the right decision about what to learn and how to learn. The teachers are responsible to develop the curiosity among the students to know to do and to learn. The learners are encouraged to think and to decide. The positive decision-making power of students is evoked. The counselling of the students plays a major role in the progress of the

student. The mentor-mentee interpersonal relationship is encouraged for the better mutual understanding and effective learning/teaching of the second language.

Techniques of the Teaching and Learning

The teaching and learning of the second language or any foreign language has become a part of the curriculum. Due to the pandemic situations, the learning and teaching has become completely digitalised than before. At present, the role of the teacher is not only the facilitator for the students but they have to behave like their friends, their second parents. They need to understand their thoughts and develop the positive interaction during the teaching of the second language. At the same time, they must motivate the students to learn what is required for them. The teacher has to make them independent and responsible. At present with all the other pressures of life, the students do not want to be dominated by the teachers to carry out their studies. Thus, the teacher as a mentor can motivate them to become autonomous, and only after this kind behaviour of the teacher, the student will take the responsibility of their study. Moreover, the student will feel responsible to achieve their goals and accomplish the objectives of the course and course outcome resulting in the development of the student. According to Freeman (1996), the teachers have the real knowledge and understanding of the environment in which they need to conduct their classes effectively to make their students comfortable and enhance their overall development.[4]

The understanding between the student and teacher strengthened when the course objective, and the course outcome is understood and decided together by the student and the teacher. This togetherness of the stakeholders during the academic development paves the way to the concern for each other. The objective of the teaching and learning focuses on the acquisition of the new knowledge along with the empathy and positive attitudes which is required in the life along with the academic development of the student. The humanistic approach can be well adopted only after the complete participation and sharing of the views for the syllabus by the stakeholders – parents, students, faculty, alumni and the industry experts. The viewpoint of the stakeholders shows the area of interest of the learners and equally the support of all the other stakeholders for defining the learning of the students. The course is thus formulated at the priority, to the interest of the learner and the requirement of the outer world so that the learners are not defeated at any step. The input and suggestions of the learners are respected. The teachers in equal collaboration with the students and parents formulate the curriculum which is respected and obeyed by each of the stakeholder. It is not like the traditional pattern of designing the syllabus where only the higher academicians design the structure and content. The collaborative work of the formulation of syllabus develops the sense of responsibility and the motivation among the students. Thus, the course syllabus and structure proposed in coordination with the stakeholders defines the target and goals that will definitely be achieved and set forth the potentialities of the learner. The humanistic approach also requires the change in the role of the teacher for the effective teaching. The teacher needs to be flexible while teaching the students but has to develop the motivation among the learners for learning the language. This teaching strategy develops the subjectivity among the teacher and learner. The teacher training is required for adapting the humanistic approach of teaching where in the teachers are only the facilitators in the class. The need to develop the interpersonal relations with the students is one of the basic requirements of this approach. Coffin (2003) states that while framing the curriculum the teachers should follow "theory of language as 'social action'"(p.11)[5]. She has also suggested that the learners should construct their knowledge of the second language on the basis of text structure, grammar experiential learning and their interpersonal relations and communication.

Besides this, the evaluation pattern of the learning varies from place to place and time to time. At one place, the language learning evaluation depends on the lexical, grammatical, phonological pattern while at other place, the orthograph matters a lot. The self-evaluation by the learners fosters the autonomy resulting in the learning through self-assessment. This leads to the gradual progression of the student and the self-satisfaction. The grading pattern by the teachers discourages the students as a result they learn only for the sake of grades and not for the knowledge. Humanistic approach tests the student by the problem-solving assignment where all the students perform their activity as per their own personal understanding. The group discussion helps the students to know the personal views of all the students thus encouraging them to learn much more than what is prescribed in their syllabus and

expected from them at that level. Besides this, the open examination fosters the discovery learning and the proper use of the freedom among the students.

In 21st century, the most efficient part of the teaching and learning is the use of innovative and flexible methods to facilitate the teaching and learning of the second language. The learning of the foreign language requires a plethora of communicative activities. The students' needs to qualify the four skills of learning the language namely, writing, speaking, reading, and listening. These four skills are developed by the sharing of the target language among the relation between teacher and student as well as student and student. Besides this, the students are equally required to interact with the people of the target language. This shows that the knowledge of the society and the interaction help the students to develop their subject-wise knowledge and the knowledge of the human values and attitudes. The empathy for the students will enable the teachers to understand the psychology of the student which promote or restrict them for learning one thing or the other. Thus, the humanistic approach of education facilitates the teacher to create the situation and use the knowledge of the student towards the development of the student. It has been found that the humanistic approach of teaching-learning is more effective in today's world where everything is changing so fast. According to Maslow, the experience is the basis of the learning, and it contributes in the behaviour of the learner and his self-actualisation. The approach focuses on the human behaviour and the human qualities like creativity, values, self-realization, choice etc. The inner self of the individual and his needs are given more importance than any other aspect of learning. As per the humanistic strategy, the native-like proficiency is not the concern in the learning of the second language. This approach promotes the acceptance of the diversity and the respect for the learner's native culture and pluricentrism.

CONCLUSION

Teaching and learning of Second language are facing several challenges in current scenario when the technology-based education has dominated the education system. The learners have different perspectives and objectives for learning the second language. Thus, the humanistic approach proposes that the language curriculum needs to be framed and evaluated through the feedback from the stakeholders. It needs to be restructured as per the needs, if required, with every new batch of students. The change in the methodology and strategies of teaching and learning brings forth the development and creativity in the education system. The active participation of the student is required for the acquisition of the second language/foreign language and the learner's self-actualisation. The humanistic approach of teaching -learning is the best way to foster the acceptance and understanding of different cultures through the learning of the different languages. The learning is best achieved in languages when there is humanistic approach between the relationship of the teacher and the student. Through this paper, I tried to point out that the humanistic and pragmatic approach will facilitate the learning of the languages under the prevailing challenging conditions due to pandemic situations. This holistic and phenomenological approach will not only bring the academic development of the learner but will also bring forth the personal development of the learner and the creation of the humanistic society.

Limitations and Future Studies

The humanistic approach of teaching and learning is too idealistic and positive. It focuses on the self -actualisation, needs, and potential for the complete development of the learner. But there are the learners who need the hard work. Thus, the concentration on their freedom or the needs works less in such situations. The teacher has to change the methodology of teaching in order to realise the effective learning by these learners. Moreover, the freedom of choice can lead the students to study the domain what they want, and they would not like to restrict themselves to the class curriculum structure. Thus, the freedom of choice under restricted curriculum has to be proposed to control the systematic follow up of the learning for long-life. The humanistic approach along with the social constructivism and cognitive constructivism can work better for the benefit of the learners and the society as a whole.

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RESEARCH ARTICLE

Biofertilizer Mixed Solid Sago Mill Waste Vermicompost (*Eisenia fetida)* and its Application to Spinach (*Amaranthus campestris*)

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ABSTRACT

Solid sago mill waste creates numerous environmental problems. To reduce the pollution effect vermicomposting the sago mill solid waste with cow dung (1: 1 ratio) using exotic earthworm (*Eisenia fetida*) along with biofertilizers (*Azospirillum, Phosphobacterium, Rhizobium*). A valuable vermicompost has been harvested after 80th day, physico chemical parameters were analysed by standard procedures. The effect of vermicompost, biofertilizer mixed vermicompost were applied to agricultural crop Amaranthus plant (*Amaranthus campestris*). Plant growth reveals high significance in E2(Vermicompost+Azospirillum) than other experimental vermicomposts and control treatments.

Keywords: biodegradable, Vermicompost, agricultural, environmental.

INTRODUCTION

Sago, a typical consumable starch as globules is gotten by handling the tubers of custard (*Manihot esculenta* cranta). Sago industry is one of the significant scope divisions in India, nearly 800 units situated in Salem District of Tamil Nadu. The handling of sago produces tremendous amounts of biodegradable dirty fluid waste which are exceptionally natural, noxious and acidic in nature (Rajesh Banu *et al*., 2006). The soil is one topmost thin and composite layer of earth and it was made up of many things like weathered rock particles, decayed plant and animal matter with varying ratios of minerals, air, water and organic material (Kamaraj Yoganathan et al., 2017). The sago manufacturing is classified below the orange category by the Tamil Nadu Pollution Control Board (Subramanian *et al*., 2010). Hence, the sago processing industry often is professed by local populations as contributing suggestively to environmental damage especially to soil biological health due to cyanide content of the residue. Among the different residues ejected from the sago factory, the solid waste called 'Thippi' is very dangerous. As such, there were no systematic studies on the extent of soil harm due to tapioca starch factory solid waste (Thippi) as well as on the positive or negative influence of these residues on crop production (Syamala *et al*., 2017). Thippi (Solid fibrous waste) discharged after the withdrawal of starch from cassava tuber is lowly in all plant essential nutrients and had a very

extraordinary C: N ratio (82:1). In order to find an appropriate alternative to decrease the environmental effluence caused by thippi, an effort was made to exchange thippi to organic manure through different traditional methods of composting (Chithra *et al*., 2013). Since the compost released nutrients in very essential, a pot maturation study for a period of one year was also conducted to estimate the extent of nutrient mineralization from sago solid waste compost to soil-plant uptake (Agamuthu *et al*., 2000).

Good quality farmyard manure (FYM) is a more valuable organic manure. Applications of vermicompost discretely or in mixture with either other carbon-based fertilizers or artificial fertilizers have been attested actually to enhance growth and yield of various plants like Urad and Soyabean (Javed and Panwar, 2013), Setariagrass (Sabrina *et al*., 2013), *Amaranthus sp*. (Uma and Malathi, 2009). The vermicomposting has been exposed to contain improved quantities of essential plant nutritional elements such as nitrogen, phosphorus, and potassium together with the biologically active substances stimulating plant growth (Lee, 1985). Hence, studies were initiated to find out probable ways to utilize the solid residue for plant nutrition in a reprocessing mode so that along with the discarding of the waste, its application in a better way also was envisaged. The present work has been designed to minimize the impact of environmental pollution due to the sago mill solid waste (Thippi)by vermicomposting with cow dung and different biofertilizers (*Azospirillum, Phosphobacterium*, *Rhizobium*). Characterization of the vermicompost concerning the parameters evaluated, and application of vermicompost to *Amaranthus campestris* growth and bio-chemical parameters were examined.

MATERIALS AND METHODS

Sample collection

The samples of sago waste collected from Varalakshmi Sago factory, Mallur, Salem district of Tamil Nadu. Cow dung was also collected from the nearby agricultural garden.

Experimental Setup

The experiments were piloted in six plastic pots (25cm diameter and 40cm height) three replication, each plastic pot 3kg of waste capacity, with a small hole at the bottom to remove the excess water. One week old urine free cow dung (CW) and sago mill solid waste Thippi (SMSWT) mixed with 1:1 ratio and also added biofertilizers (*Azospirillum*, *Phosphobacterium*, and *Rhizobium*) where added 1gm / kg of compost (Subramaniam, 2006) Table1. The substrates were kept 20 days for pre-decomposing. Exotic earthworms (*Eisenia fetida*) 30nos where introduced to each experimental tubs. Approximately 60 – 80% of moisture level was maintained throughout the experimental period by the sprinkle of a sufficient quantity of tap water.

Physico-chemical analysis

The physicochemical parameters of vermicompost during the 80th day experiments were analyzed for standard methods. The pH of vermicompost samples was determined using a double DH_2O suspension of compost in the ratio of 1:10 (w/v) analyzed in Digital pH meter (Vasanthi *et al*., 2014), the total organic carbon content was estimated using the method of (Abdullah and Chin, 2010). The nitrogen was estimated by the Micro Kjeldahl method (Mohee *et al*., 2008; Unmar and Mohee, 2008). Phosphorus was detected by the colorimetric method (John, 1970). Potassium was determined after digesting the sample in diacid mixture (concentration HNO_3; concentration $HClO_4$, 4:1 v/v), by Flame Photometer (Bansal and Kapoor, 2000). Sulfur, Zinc, Boron, and Iron were measured by the diacid digest using an atomic absorption spectrophotometer (Vasanthi *et al*., 2014).

Plot Preparation

The seed of *Amaranthus campestris* was sown manually in areas of the open field. The experiment was arranged in the Completely Randomized Block Design (CRD) with three replications. Field plot area was 60 x 60 cm and the distance for inter between gaps of plots 15cm,respectively. The plot was then watered uniformly and left for a day.

Plant Selection and Seed Sowing

The seed of *A. campestris* species was obtained from Priya Agro Farm, Namakkal, and Tamil Nadu. 5g of seeds weight were selected for sowing. The seeds were spread in each plot maintaining equal distance between the seeds and water was sprinkled evenly. Plots were labelled as T0- Control, T1, T2, T3, T4,and T5. Vermicompost was applied in T1,Vermicompost mixed biofertilizers T2 (*Azospirillum*), T3 (*Phosphobacterium*), T4 (*Rhizobium*), and T5 (*Azospirillum* + *Phosphobacterium* + *Rhizobium*).

Application of Fertilizers

After germination of *A. campestris* seeds in all the five plots, while 200gms of prepared vermicompost and biofertilizers was applied to plots T1 to T5 at an interval of once in 3 days.

Sampling and Data Collection

Spinach plant (*A.campestris)* growth parameters and Chlorophyll were recorded on the 15th date. A total of plants were selected randomly from each treatmentsfor the assessment of average Shoot Length (cm), Root Length (cm), Fresh Plant Weight (g), Dry Plant Weight (g), Dry Matter (%), Moisture (%), Leaf Length (cm), Leaf Breadth (cm), Chlorophyll A, B, and Total (mg/g). Plant's height was recorded using a scale. Fresh and dry plant weight noted were using a weighing balance. The chlorophyll content was analyzed using (Lichtenthaler, 1987).

Statistical analysis

The experimental data were expressed as the mean of five times replication ± standard deviation (SD). The difference in Physico-chemical parameters of sago waste vermicompost experiments with biofertilizers and treatment on *Amaranthus campestris* plants physical and biochemical with control was statistically computed using One-Way Analysis of Variance was used to define the statistically significant. Tukey's honestly significant different (HSD) tests at

$p < 0.05$ significance level was applied.

RESULT AND DISCUSSION

The nutrient content of sago waste and cow dung was given in the Table.2. The pH of the sagomill solid waste vermicompost increased progressively by the secretion of calciferous gland of earthworms during the experimental period. The tolerating extreme pH and temperature for the earthworm species *E. fetida* (Tripathi and Bhardwaj, 2004). The change in pH after vermicomposting must be due to mineralization of the nitrogen and phosphorus into nitrites/nitrates and orthophosphates and bioconversion of the organic material into intermediate species of organic acids (Ndegwa *et al*., 2000; Khwairakpam and Bhargava, 2009).

Vermicomposting caused the highest changes in EC of five experimental sources, E1 showed high EC and lowest EC was found in E3 experiment. The electrical conductivity reflects the salinity of an organic amendment. The increases of EC through vermicomposting is also informed by others (Venkatesh and Evera, 2008; Vig *et al*., 2011). The upsurge in EC could be due to the loss of organic matter and the discharge of different mineral salts in available forms, such as phosphate, ammonium, potassium, etc (Venkatesh and Eevera 2008; Kaviraj and Sharma, 2003; Vig *et al*., 2011).
The organic carbon composition of different vermicomposts varied according to the initial substrates used for decomposition. Organic carbon (OC) concentration reduced during decomposition regardless of the substrates used. The organic carbon was higher in E1 and lowest in E4. Kale, (1998) reported that in the decomposition process of carbon was transformed into CO_2 and was slightly lost to generate energy for decomposition. Raghavendra and Bano, (2001) also was observed in the chemical composition of the waste influenced by the rate of organic carbon mineralization. The nitrogen (N) increased final decomposition and the highest nitrogen was observed in E2 (3.75%) than other experiments. Among the mixture of different bio-fertilizers, the nitrogen content was increased by the proportion of sago waste. The excretory products of earthworms increase the N level in the substrate (Suthar and

Singh, 2008), and the addition of N-fixing bacteria to the compost medium enhances total nitrogen content (Kaushik and Garg, 2004). The overall phosphorus (P) was also significant in all the treatments, and the concentration of phosphorus varied according to the P concentration of the substrates. However, the E3 (2.67%) experiment showed higher P concentration over the others. Sterilized and Sterilized, (2000) reviewed that the phosphorus solubilizing microorganisms enhance the phosphatase activity through decomposition resulting from the greater mineralization process and upturns the P concentration in the final vermicompost. Highest potassium was observed in the E4 (3.02%), whereas least K content was in E3 (2.33%). Subramanian *et al*., (2010), states that K content was high in sago waste blended with cow dung manure at equal proportions (3.3 – 3.6%). However, vermicomposting of the sugar mill sludge by *E. fetida* has shown an upsurge of N, P, and K when modifying with biogas plant slurry (Sangwan *et al*., 2008).

Sulphur content was maximum in all the experimental vermicompost samples which cause mortality of earthworms during the experimental period. The sulphur content of the experiments was increased in El and decreased in E5. Subramanian *et al*., 2010, observed 87mg/kg of solid sago mill waste vermicompost. The boron content was increased in the all vermicomposting treatments irrespective of the proportions of biofertilizers or cow dung mixed with sago waste. The increase in the boron content was prominent in the E1 (0.66 ppm) treatment of sago waste and cow dung. An elevated Zn was also observed in E3 (0.55 ppm) increased significantly. Yadav and Garg, (2010) reported that zinc concentrations were 20-110% higher in vermicompost of the food industry sludge. Maximum iron (Fe) content was observed in E2 (8.60 ppm) and minimum in E1(6.43ppm). The increased Fe content in E2 may be due to the mortality of earthworms during the experimental period. Sharma and Garg, (2018) reported 31 – 136% increment in Fe content after 105 days of worm activity in the waste substrate (cow dung, rice straw, and paper waste). Song *et al*., (2014) also reported that the effects of vermicomposting on heavy metals can be wide-ranging attributed to several earthworm activities and feedstock superiority. Earthworm species differ in their capability to uptake heavy metals in their body tissues (Ramalingam and Ranganathan, 2001).

The highest *Amaranthus campestris* plant shoot length (18.54 cm) was recorded in T2 of vermicompost and *Azospirillum* in compared to control T0. Maximum root growth in T2(4.72cm) followed by T0(4.090cm) and minimum in T4(3.72cm). Enhanced root growth was probably due to vermicompost improved the soil's physical properties particularly soil porosity, structure, water holding capacity and supplied other plant growth-promoting substances. Thus the application of vermicompost significantly increased plant growth by improving soil physical properties (Jahan *et al*., 2014)(Figure 1). The highest fresh weight per plant (0.62g) was recorded in T4group (0.60gm), followed by T5(0.59gm). The enhanced plant growth may be due to the beneficial microbes in the biofertilizers and plant growth regulators and other plant growth influenced factors present in the vermicompost (Grapeelli *et al*., 1987). The increased plant growth in all vermicompost treated plants (T1 to T5) may be directly linked with the photosynthetic and starch production(Curran *et al*., 1995)(Figure 3).

Among the chlorophyll content an elevated chlorophyll A was observed in T3(2.18mg/g), whereas in T2 Chlorophyll B (2.35mg/g) and Total chlorophyll (4.40mg/g). The chlorophyll content of *A.campestris* elevated gradually from T1 to T5 upon the beneficia nutrient level in the biofertilizer mixed vermicompost. Filella *et al*., (1995), observed that chlorophyll contentgave an indirect estimation of nutrient status, because leaf nitrogen level is incorporated with chlorophyll pigments. During plants vegetative growth period the total chlorophyll content increases upto flowering time and then its level reduces in reproductive and senescence periods (Riccardi *et al*., 2014)(Figure 4).

CONCULUSION

The present study reveals, that the stimulation of plant growth may depend mainly on the biological characteristics of vermicomposting. However, detailed aspects related to identifying the suitable biofertilizers with vermicompost

and soil in order to maximize yield of *A. campestris*. Vermicompost application can improve net production and thus net gain, save cultivable lands from chemical fertilizers and land pollutants.

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Table 1 Pre-decomposed substrate was divided into five combinations with biofertilizers

Experiments	Sago Solid Waste + Cow Dung (Ratio)	Biofertilizers (1gm/kg)
E1	1 : 1	-
E2	1 : 1	*Azospirillum*
E3	1 : 1	*Phosphobacterium*
E4	1 : 1	*Rhizobium*
E5	1 : 1	*Azospirillum + Phosphobacterium + Rhizobium*

Table 2.Nutrient status of Raw Sago mill solid waste and Cow dung

Parameter	Sago waste	Cow dung	P value	F value
pH	6.31±0.15	7.72±0.07	0.0001	4.59
EC	3.11±0.36	2.22±0.43	0.0514^{ns}	1.427
Organic carbon	42.53±2.73	55.60±1.90	0.0024	2.065
Nitrogen	0.72±0.14	1.61±0.24	0.0026	2.939
Phosphorous	0.36±0.05	0.62±0.08	0.0044	4.774
Potassium	0.27±0.05	0.62±0.08	0.0015	2.560
Sulphur	0.85±0.06	1.48±0.19	0.0027	10.028
Zinc	3.36±0.18	5.67±0.36	0.0003	4.000
Boron	0.49±0.10	0.79±0.05	0.0048	4.000
Iron	1.27±0.07	2.40±0.11	<0.0001	15.011

Table-3.Physico-chemical analysis of 80th day vermicompost sample.

Exp.	pH	EC	OC	N	P	K	S	Zn	B	Fe
E1	6.97 ±0.12	6.41 ±1.42	47.57 ±0.53	2.89 ±0.35	2.46 ±0.18	2.79 ±0.41	1.15 ±0.05	3.54 ±0.17	0.86 ±0.06	4.43 ±0.26
E2	7.95 ±0.37	2.97 ±0.35	47.05 ±0.58	3.75 ±0.60	2.57 ±0.47	2.47 ±0.33	1.12 ±0.04	4.42 ±0.17	0.53 ±0.15	4.40 ±0.22
E3	8.26 ±0.32	3.54 ±0.73	44.44 ±0.33	3.07 ±0.50	2.67 ±0.63	2.33 ±0.56	1.06 ±0.04	3.55 ±0.17	0.63 ±0.20	4.66 ±0.32
E4	8.02 ±0.33	2.78 ±0.61	44.39 ±1.28	2.83 ±0.44	2.44 ±0.52	3.02 ±0.38	1.25 ±0.09	0.52 ±0.16	0.59 ±0.22	4.57 ±0.23
E5	7.93 ±0.20	5.91 ±1.13	46.61 ±0.20	3.08 ±0.66	2.17 ±0.51	2.64 ±0.47	1.03 ±1.79	3.38 ±0.19	1.44 ±0.22	4.32 ±0.19

Table 4: Growth of *Amaranthus campestri* on the 15th days of culture

Days	Total length	Shoot Length	Root Length	Fresh weight	Dry weight	Chlorophyll		
						A	B	Total
Control (T0)	21.002 ±1.127	16.912 ±1.476	4.090 ±0.715	0.60342 ±0.036527	0.049886 ±0.00153	1.693 ±0.199	1.100 ±0.119	2.793 ±0.258
T1	23.220 ±1.163	17.920 ±0.920	4.045 ±0.336	0.291 ±0.036	0.0291 ±0.0036	2.060 ±0.183	1.768 ±0.175	3.828 ±0.348
T2	22.660 ±1.674	18.540 ±0.799	4.720 ±0.311	0.5187 ±0.0821	0.0419 ±0.0026	2.054 ±0.184	2.350 ±0.251	4.404 ±0.430
T3	21.664 ±1.524	17.910 ±1.066	3.754 ±0.492	0.4087 ±0.0336	0.0312 ±0.0037	2.180 ±0.269	1.378 ±0.297	3.558 ±0.566
T4	22.080 ±1.942	18.360 ±1.573	3.720 ±0.449	0.6274 ±0.0748	0.0574 ±0.0066	2.098 ±0.204	2.216 ±0.127	4.314 ±0.330
T5	22.980 ±2.249	18.380 ±1.669	4.600 ±0.596	0.5911 ±0.0321	0.0502 ±0.0030	2.024 ±0.072	2.296 ±0.326	4.320 ±0.392

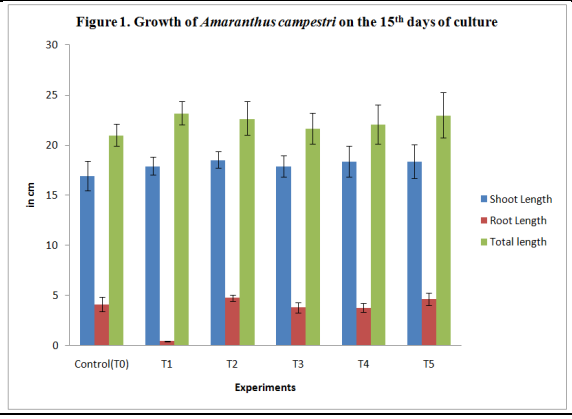

Figure 1. Growth of *Amaranthus campestri* on the 15th days of culture

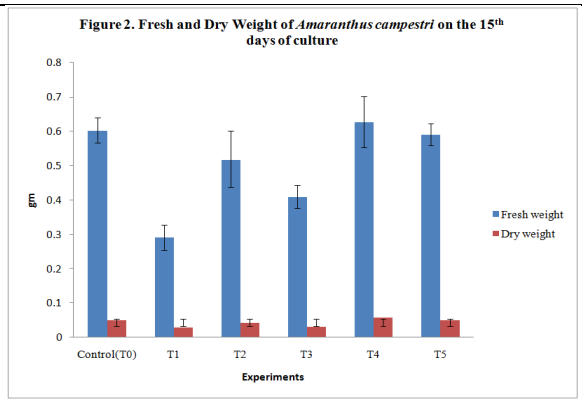

Figure 2. Fresh and Dry Weight of *Amaranthus campestri* on the 15th days of culture

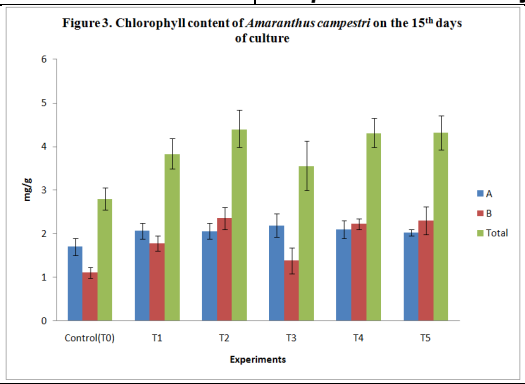

Figure 3. Chlorophyll content of *Amaranthus campestri* on the 15th days of culture

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RESEARCH ARTICLE

GC MS Study of One Ayurvedic Formulation "Brihat Vaiswanara Churnam

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ABSTRACT

The present work deals with the GC MS analysis of one Ayurvedic digestive medicine, Brihat vaiswanara churnam. The medicine was procured from a standard Ayurvedic vendor at Chennai, India and was subjected to GC MS analysis following standard protocol. Results: The molecules present in Brihat Vaswanara churnam, such as, Asarone, 2(1H)-Benzocyclooctenone, decahydro-10a-methyl-, trans-, Methyl 4,7,10,13,16-docosapentaenoate, Sulfurous acid, butyl heptadecyl ester, trans-13-Octadecenoic acid, Piperine, Behenic alcohol, Z-10-Methyl-11-tetradecen-1-ol propionate, Ursodeoxycholic acid have important medicinal roles that could support the functions of this medicine towards curing digestion related ailments. It can be concluded that Brihat Vaswanara churnam indicates its potency to serve as good digestive medicines as shown by the GC MS profile.

Keywords: GC MS, Brihat Vaiswanara Churnam, Ayurvedic, Asarone, Piperine, Behenic alcohol

INTRODUCTION

Brihat Vaiswanara Churnam is an Ayurvedic herbal powder, prescribed for digestive tract disorders such as weak digestion, abdominal colic, bloating of abdomen, tumor, mal-absorption syndrome, Irritable bowel syndrome altering diarrhoea, constipation and as laxative. The dosage of this medicine is 5 g once or twice a day along with hot water or buttermilk or as advised by Ayurvedic doctor. For children below 5 years of age, the dose is 1 to 2 g once or twice a day before or after food or as advised by Ayurvedic practitioner. For children of 5 – 12 years of age, dose is – 2-5 grams once or twice a day before or after food, as advised by Ayurvedic doctor. It is best taken along with hot water or butter milk.

This medicine consist of 0.313 g each of *Plumbago zeylanica, Aconitum heterophyluum, Ferula assa-foetida, Sausserea lappa,* Unaqua Sodium Chloride (kiln-fired rock salt), *Acorus calamus, Piper longum, Inula racemosa, Cleodendrum serratum, Carum copticum, Zingiber officinale, Embelica ribes, Piper nigrum, Leonotis nepetifolia, Scindapsus officinalisand 5 g of Terminalia chebula. All the above ingredients are separately powdered and mixed together to prepare this medicine. There is a need to scientifically validate the Ayurvedic and other forms of complementary and alternative medicines, because although in practice for thousands of years, their efficacy has not been established. Some work in this regard is available and much more need be done [1-29] Patil, 2016 has evaluated the phytochemical and pharmacognostic aspects of Vaishwanara churna [30].*

MATERIALS AND METHODS

Brihat Vaishwanara churnam was obtained from standard Ayurvedic vendor at Chennai and was subjected to GC MS analysis by standard procedure.

Instrument: Gas chromatography (Agilent: GC: (G3440A) 7890A. MS MS: 7000 Triple Quad GCMS,) was equipped with Mass spectrometry detector.

Sample Preparation

100 micro lit sample Dissolved in 1 ml of suitable solvents. The solution stirred vigorously using vortex stirrer for 10 seconds. The clear extract was determined using gas-chromatography for analysis.

GC-MS protocol

The GC MS Column consisted of DB5 MS (30mm×0.25mm ID ×0.25 μm , composed of 5% phenyl 95% methyl poly siloxane), Electron impact mode at 70 eV; Helium (99.999%) was used as carrier gas at a Constant flow of 1ml/min Injector temperature 280 °C; Auxilary Temperature : 290°C Ion-source temperature 280 °C. The oven Temperature was programmed from 50 °C (isothermal for 1.0 min), with an increase of 40°C/min, to 170°C C (isothermal for 4.0 min), then 10°C/min to 310°C (isothermal for 10min) fragments from 45 to 450 Da. Total GC running time is 32.02 min. The compounds are identified by GC-MS Library (NIST & WILEY).

RESULTS

The GC MS profile of Brihat Vaiswanara churnam is represented in Figure 1. Table1 indicates the retentions time, types of possible compound, their molecular formulae, molecular mass and percentage peak area as shown in the GC MS profile of Brihat Vaiswanara churnam. The identification of metabolites was accomplished by comparison of retention time and fragmentation pattern with mass spectra in the NIST spectral library stored in the computer software (version 1.10 beta, Shimadzu) of the GC-MS along with the possible pharmaceutical roles of each bio-

molecule as per Dr. Duke's Phytochemical and ethnobotanical data base (National Agriculture Library, USA) and others as shown in Table 1 [31].

DISCUSSION

The molecules present in Brihat Vaswanara churnam, such as, Asarone, 2(1H)-Benzocyclooctenone, decahydro-10a-methyl-, trans-, Methyl 4,7,10,13,16-docosapentaenoate, Sulfurous acid, butyl heptadecyl ester, trans-13-Octadecenoic acid, Piperine, Behenic alcohol, Z-10-Methyl-11-tetradecen-1-ol propionate, Ursodeoxycholic acid have important medicinal roles that could support the functions of this medicine towards curing digestion related ailments.

CONCLUSION

It is concluded from the above results that Brihat vaswanara chrunam contains some important biomolecules which help in the cure of digestive ailments.

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COMETING INTERESTS: The authors declare that no competing of interest exists among them.

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Table1. Indicates the retentions values, types of possible compound, their molecular formulae, molecular mass, peak area and their medicinal roles of each compound as shown in the GC MS profile of Brihat Vaishwanara Churnam

Sl. No	Retention Time	Compound Name	Mol. Formula	Mol. Weight	% Peak Area	Possible medical Role
1	8.51	Bicyclo[5.2.0]nonane, 2-methylene-4,8,8-trimethyl-4-vinyl-	C15H24	204.2	0.76	Not known
2	9.52	1-Nonylcycloheptane	C16H32	224.3	1.31	Not known
3	9.62	Dodecane, 1-fluoro-	C12H25F	188.2	1.27	Not known
4	9.79	Naphthalene, 1,2,3,5,6,8a-hexahydro-4,7-dimethyl-1-(1-methylethyl)-, (1S-cis)-	C15H24	204.2	0.96	Not known
5	10.93	Asarone	C12H16O3	208.1	5.23	antifungal
6	13.02	2(1H)-Benzocyclooctenone, decahydro-10a-methyl-, trans-	C13H22O	194.2	0.70	Catechol-O-Methyl-Transfearse inhibitor, Increases Glutathione-s-Transferase Activity, Decrease Glutamate Oxaloacetate transaminase activity, Decreases Glutamate pyruvate transaminase, Glycosyl transferase inhibitor, Glutathione-S-Transfearse inhibitor, Increases glyoxalate transamination, Reverse transcriptase inhibitor, Anti 5-HT, Anti HIV integrase, Aryl hydrocarbon hydroxylase inhibitor, HIF 1 alpha inhibitor, increases tyrosine hydroxylase activity, Suppress HMG Co-A reductase activity, Tyrosine hydroxylase activator, 11Beta HSD inhibitor.
7	13.64	Eudesma-5,11(13)-dien-8,12-olide	C15H20O2	232.1	3.56	Not known
8	14.03	Methyl 4,7,10,13,16-docosapentaenoate	C23H36O2	344.3	3.35	Catechol-O-methyl transferase inhibitor, Methyl donor, Methyl guanidine inhibitor

9	14.08	Card-20(22)-enolide, 3,5,14,19-tetrahydroxy-, (3.beta.,5.beta.)-	C23H34O6	406.2	0.71	Not known
10	15.72	Cyclopentane, 1-pentyl-2-propyl-	C13H26	182.2	3.16	Not known
11	16.37	5-Eicosene, (E)-	C20H40	280.3	0.68	Not known
12	16.65	Sulfurous acid, butyl heptadecyl ester	C21H44O3S	376.3	8.39	Acidifier, Arachidonic acid Inhibitor, Increases Aromatic Amino acid decarboxylase activity, Inhibits production of uric acid, Urine acidifier
13	17.00	11,13-Dimethyl-12-tetradecen-1-ol acetate	C18H34O2	282.3	1.05	Oligosaccharide provider
14	17.24	Butyl 6,9,12-hexadecatrienoate	C20H34O2	306.3	0.79	Not known
15	17.64	2-Propenoic acid, 3-phenyl-, cyclohexyl ester	C15H18O2	230.1	2.04	Not known
16	19.04	Behenic alcohol	C22H46O	326.4	1.37	Alcohol dehydrogenase inhibitor
17	20.51	trans-13-Octadecenoic acid	C18H34O2	282.3	0.79	Acidifier, Arachidonic acid inhibitor, Increases aromatic amino acid decarboxylase activity, inhibit uric acid production
18	20.55	1-Decanol, 2-hexyl-	C16H34O	242.3	1.94	Not known
19	21.25	Heptadecane, 2,6,10,15-tetramethyl-	C21H44	296.3	1.05	Not known
20	21.67	Piperine	C17H19NO3	285.1	1.39	Radio-protective, immune-modulatory, anti-tumor, antidepressant, anticonvulsant, anti-nociceptive, anti-arthritic, helps in absorption of selenium, vitamin B and Beta carotene and other nutrients.
21	22.59	Octatriacontyl pentafluoropropionate	C41H77F5O2	696.6	0.93	Not known
22	23.23	Z-10-Methyl-11-tetradecen-1-ol propionate	C18H34O2	282.3	1.15	Increases Zinc bioavailability, oligosaccharide provider, Catechol-O-methyl transferase inhibitor, Methyl donor, Methyl guanidine inhibitor
23	24.30	Ursodeoxycholic acid	C24H40O4	392.3	0.82	Acidifier, arachidonic acid

						inhibitor, increases aromatic amino acid decarboxylase activity, inhibits production of uric acid
24	25.12	9,19-Cyclochloestene-3,7-diol, 4,14-dimethyl-, 3-acetate	C31H52O3	472.4	1.73	Not known
25	25.32	Lup-20(29)-en-3-ol, acetate, (3.beta.)-	C32H52O2	468.4	9.64	Not known
26	26.95	Trimyristin	C45H86O6	722.6	45.20	Not known

Qualitative Compound Report

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Comment			

User Chromatogram

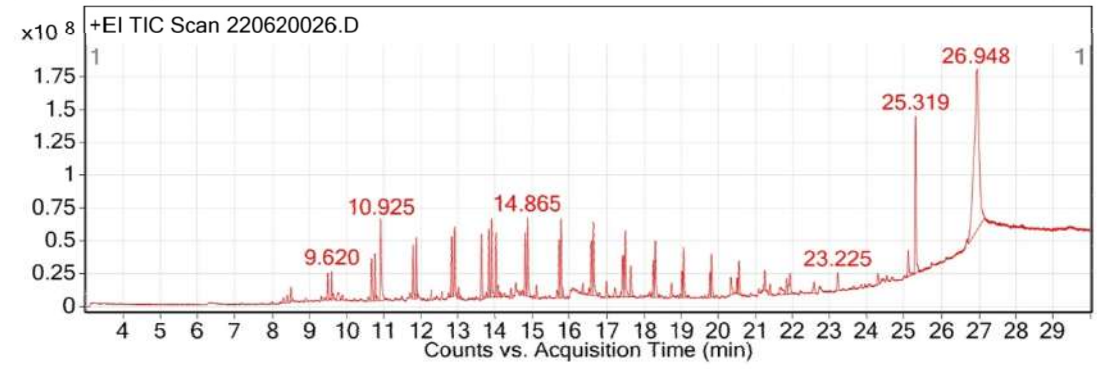

Figure 1. Shows the GC MS profile of Brihat Vaiswanara Churnam

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REVIEW ARTICLE

A Review Nanomondes: An Innovative Drug Delivery System

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ABSTRACT

Effective targeted drug delivery systems have been a dream for a long time, but it has been largely frustrated by the complex chemistry that is involved in the development of new systems. The invention of nanosponges has become a significant step toward overcoming these problems. Nanosponges are tiny sponges with a size of about a virus, which can be filled with a wide variety of drugs. These tiny sponges can circulate around the body until they encounter the specific target site and stick on the surface and begin to release the drug in a controlled and predictable manner. Because the drug can be released at the specific target site instead of circulating throughout the body it will be more effective for a particular given dosage. Another important character of these sponges is their aqueous solubility; this allows the use of these systems effectively for drugs with poor solubility.

Keywords: Nanomondes, Targeted drug delivery systems, Cross-linker the particles

INTRODUCTION

Targeting the delivery of drugs has long been a problem for medical researchers - how to get them to the right place in the body and how to control the release of the drug to prevent overdoses. The developments of new and complex molecules called nanosponges have the potential to solve these problems. Nanosponges are a new class of materials and made of microscopic particles with few nanometers wide cavities, in which a large variety of substances can be encapsulated. These particles are capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water soluble molecules (1).

Nanosponges are tiny mesh-like structures that may revolutionise the treatment of many diseases and early trials suggest this technology is up to five times more effective at delivering drugs for breast cancer than conventional methods (2). To get intended result, targeting drug delivery systems have been an ambition for a prolonged period. In the beginning, Nanosponge drug delivery system appeared only as a topical delivery system, but in the 21st century, Nanosponges can be administered by oral as well as intravenous (IV) route [1].

Nanosponge is a modern category of material and is made up of tiny particles with a narrow cavity of few nanometers. These narrow cavities can be filled with various types of substances. These tiny particles are having a capability due to which it is able to carry both hydrophilic and lipophilic drug substance and can increase the stability of poorly water-soluble drug substance or molecules [2]. The nanosponges are a three-dimensional scaffold (backbone) or network of polyester that are capable of degrading naturally. These polyesters are mixed with a crosslinker in a solution to form Nanosponges. Here, the polyester is generally biodegradable, so it breaks down in the body moderately. Once the scaffold of nanosponges breaks down it releases the drug molecules which is loaded, in a derogatory fashion. The nanosponge is about the size of a virus with a 'backbone' (a scaffold structure) of naturally degradable polyester. The long length polyester strands are mixed in solution with small molecules called cross-linkers that have an when it breaks up in the body, the drug can be released on a known schedule (2). The nanosponges are encapsulating type of nanoparticles which encapsulates the drug molecules within its core. By the method of associating with drugs, the nanoparticles can be classified into encapsulating nanoparticles, complexing nanoparticles and conjugating nanoparticles. The first type is represented by nanosponges and nanocapsules.

Nanosponges such as alginate nanosponge, which are sponge- like nanoparticles containing many holes that carry the drug molecules. Nanocapsules such as poly(isobutyl-cyanoacrylate) (IBCA) are also encapsulating nanoparticles. They can entrap drug molecules in their aqueous core. The second category is Complexing nanoparticle, which attracts the molecules by electrostatic charges. The third type is Conjugating nanoparticle, which links to drugs through covalent bonds (3). These nanosponges represent a novel class of nanoparticles usually obtained by natural derivatives. As compared to the other nanoparticles, they are insoluble both in water and organic solvents, porous, non toxic and stable at high temperatures up to 300°C.

Mechanism of drug release from nanosponges

Since the nanosponges have an open structure (in the surrounding of nanosponges they do not have any continuous membrane), the active substance is added to the vehicle in an encapsulated form. The encapsulated active substance is able to move freely from the particles into the vehicle until the vehicle gets saturated and the equilibrium is obtained. As soon as the product is applied on to the skin, the vehicle containing the active ingredient gets unsaturated causing a disturbance in the equilibrium. Thus, the flow of active substances from nanosponge particles into vehicles starts to epidermis until the vehicle is either absorbed or dried. Even after the retention of the nanosponge particles on the surface of skin i.e. the stratum corneum, the release of active substance continues to skin for a long period of time.

Advantages of nanosponges

- Increase aqueous solubility of the poorly water-soluble drug.
- Nanosponges can release the drug molecules in a predictable fashion.
- Because of their tiny pore size (0.25 µm), bacteria cannot penetrate the nanosponges and they act like a self-sterilizer.
- Nanosponges drug delivery system are non-irritating, non- mutagenic and non-toxic.
- Nanosponges help to remove the toxic and venom substance from the body.
- Nanosponges drug delivery system minimize side effect.
- Increase formulation stability and enhance the flexibility of the formulation.
- Reduce dosing frequency.
- Better patient compliance.

- Nanosponges complexes are stable over wide range of pH (i.e. 1-11) and a temperature of 130 °C [4-6].

Disadvantages of nanosponges

- Nanosponges have the capacity of encapsulating small molecules, not suitable for larger molecules.

Dose dumping may occur at times [7]

SYNTHESIS OF NANOSPONGES

Solvent method

Mix the polymer with a suitable solvent, in particular in a polar aprotic solvent such as dimethylformamide, dimethylsulfoxide. Then add this mixture to excess quantity of the cross-linker, preferably in crosslinker/polymer molar ratio of 4 to 16. Carry out the reaction at temperature ranging from 10°C to the reflux temperature of the solvent, for time ranging from 1 to 48h. Preferred crosslinkers are carbonyl compounds (Dimethyl carbonate & Carbonyldiimidazole) (5).

After completion of the reaction, allow the solution to cool at room temperature, then add the product to large excess of bidistilled water and recover the product by filtration under vacuum and subsequently purify by prolonged soxhlet extraction with ethanol. Dry the product under vacuum and grind in a mechanical mill to obtain homogeneous powder (16).

Ultarsound-Assisted synthesis

In this method nanosponges can be obtained by reacting polymers with cross-linkers in the absence of solvent and under sonication. The nanosponges obtained by this method will be spherical and uniform in size (1). Mix the polymer and the cross-linker in a particular molar ratio in a flask. Place the flask in an ultrasound bath filled with water and heat it to 90°C. Sonicate the mixture for 5hours. Then allow the mixture to cool and break the product roughly. Wash the product with water to remove the non- reacted polymer and subsequently purify by prolonged soxhlet extraction with ethanol. Dry the obtained product under vacuum and store at 25°C until further use (1,16).

Loading of drug into nanosponges

Nanosponges for drug delivery should be pre- treated to obtain a mean particle size below 500nm. Suspend the nanosponges in water and sonicate to avoid the presence of aggregates and then centrifuge the suspension to obtain the colloidal fraction. Separate the supernatant and dry the sample by freeze drying (16). Prepare the aqueous suspension of Nanosponge and disperse the excess amount of the drug and maintain the suspension under constant stirring for specific time required for complexation. After complexation, separate the uncomplexed (undissolved) drug from complexed drug by centrifugation. Then obtain the solid crystals of nanosponges by solvent evaporation or by freeze drying (5,16).

Crystal structure of nanosponge plays a very important role in complexation with drug. A study revealed that paracrystalline nanosponges showed different loading capacities when compared to crystalline nanosponges. The drug loading is greater in crystalline nanosponges than paracrystalline one. In poorly crystalline nanosponges, the drug loading occurs as a mechanical mixture rather than inclusion complex (11).

FACTORS INFLUENCE NANOSPONGE FORMATION

Type of polymer

Type of polymer used can influence the formation as well as the performance of Nanosponges. For complexation, the cavity size of nanosponge should be suitable to accommodate a drug molecule of particular size.

Type of drugs

Drug molecules to be complexed with nanosponges should have certain characteristics mentioned below (23).

- Molecular weight between 100 and 400
- Drug molecule consists of less than five condensed rings
- Solubility in water is less than 10mg/mL
- Melting point of the substance is below 250°C

Temperature

Temperature changes can affect Drug / Nanosponge complexation. In general, increasing in the temperature decreases the magnitude of the apparent stability constant of the Drug/Nanosponge complex may be due to a result of possible reduction of drug/nanosponge interaction forces, such as van-der Waal forces and hydrophobic forces with rise of temperature (24).

Method of preparation

The method of loading the drug into the nanosponge can affect Drug/Nanosponge complexation. However, the effectiveness of a method depends on the nature of the drug and polymer, in many cases freeze drying was found to be most effective for drug complexation (22).

Degree of substitution

The complexation ability of the nanosponge may be greatly affected by type, number and position of the substituent on the parent molecule (22).

Method of preparation

The method of drug loading into the nanosponges can cause a change in the complexation of drug and the nanosponges. Although, the success of a method mainly depends on the nature or the characteristics of the drug and polymer; in some cases, freeze drying has also been known to affect the drug and nanosponge complexation.

Characterization of nanosponges

The characterization methods for the complexed drug/nanosponges are listed below:

Solubility studies

Inclusion complexes is a technique by which can determine the solubility and bioavailability of the drug. This technique is the most widely approached technique for analysis of the inclusion complexes of nanosponges. Degree of completion can be known by the plot of phase solubility. Solubility studies are conducted to access the pH of the drug, solubilization outline and to evaluate the factors affecting drug solubility [16].

Microscopic study

Microscopic studies of nanosponges/drug can be conducted by using scanning electron microscope and transmission electron microscope. Inclusion complex formation is indicated by the difference in the crystallization state and the product seen under an electron microscope.

Zeta potential determination

Zeta potential can be defined as the difference of potential between two layers (dispersion medium and immobile layer) of fluid locked up with dispersed particles. Zeta potential is the major key indicator for the stability of the colloidal dispersion. By adding extra electrode on particle size equipment or zeta seizer, the zeta potential can be measured. Higher the value of zeta potential of a colloidal dispersion more is its stability.

Thermodynamical method

If any changes occur in drug molecules or particles undergoes some changes earlier then the thermal degradation of nanosponges it can be determined by the thermo-chemical method. The changes of drug particles can be melting, evaporation, oxidation and decomposition and polymeric changes. The changes in the drug molecules indicate the formation of a good complex.

Particle size and polydispersity

Particles size is determined by the process of dynamic light scattering using 90Plus particle size determining software. Dynamic light scattering (DLS) is defined as a technique used to find out the size distribution profile of nanoparticles. At last, the final diameter of the particles and poly-dispersity index (PDI) can be found.

Thin layer chromatography (TLC)

TLC can be defined as a technique which can be used to separate the non-volatile or evaporative mixture. In this technique, if the Rf value of a particular drug molecule is of an acceptable range then it is helpful in recognizing the formation of a complex between drug and nanosponges.

Infrared spectroscopy

The interaction between nanosponges and the drug in the solid state can be determined by using infrared spectroscopy. Nanosponge bands can slightly change during formation of complexes. Few guest molecules attached in the complexes which are less than 25%, the drug spectrum can be easily masked by the spectrum of nanosponges. The technique is not appropriate to identify the inclusion complex over the other methods [17].

Loading efficiency

The loading efficiency of a nanosponge particle can be determined by the estimation of drug loaded into the nanosponge using UV spectrophotometer and high-performance liquid chromatography method for the nanosponges. The loading efficiency of nanosponges can be calculated by using the following equation.

$$\mathbf{LE} = \frac{\text{Actual drug content in nanosponges}}{\text{Theoretical drug content}} \text{ X } 100$$

Nanosponges for drug delivery

Nanosponges can carry the water-insoluble drug because of their tiny porous structure. To increase the dissolution rate, solubility and permeability of drug nanosponges complexes play a major role. This is reported that β-cyclodextrine based nanosponges are three or five times more effective to deliver the drug to the targeted site. Nanosponges are generally solid in nature and can be prepared for oral, parental, topical and inhalation dosage form. For the preparation of tablet, capsule i.e. oral administration the nanosponges complexes are dissolved in a suitable excipient like lubricants, diluents and anti-cracking agent.

Nanosponges for cancer therapy

Most challenging works nowadays in the pharmaceutical field is the delivery of anticancer drug because of their low solubility. In one article they claim that nanosponge's complex is three times more effective to reduce the growth of tumor then direct injection. The nanosponge's complex load with a drug and expose a targeting peptide that fastens tightly with a radiation-induced cell upper layer on the tumor receptor. When nanosponges confront the tumor cell they stuck on the surface of tumor cell and start to release the drug molecules. The advantage of targeting drug delivery is to get a more effective therapeutic effect at the same dose and with minimized side effect [21].

Nanosponges for delivery of protein

To study the encapsulating capacity of β-cyclodextrin-based nanosponges, bovine serum albumin (BSA) was used as a model protein. Protein solution of bovine serum albumin (BSA) is not stable so they are stored in lyophilized form. Proteins can convert to denatured on lyophilization from its native structure. For the formulation and development of protein, the major drawback is that to maintain its native structure and long-term storage during and after processing. For delivery of the protein like Bovine serum albumin (BSA) with the cyclodextrine based, nanosponges can increase the stability of these proteins. Nanosponges have also been used for immobilization of enzyme, encapsulation of protein, for controlled delivery and stabilization [22].

Role of nanosponges for treatment of fungal infections

Fungal infections of the skin are one of the dangerous diseases in worldwide [23]. Topical therapy is an attractive choice for the treatment of the coetaneous infections due to various advantages such as targeting of drugs to the direct site of infection and reduction of systemic side effects. Econazole nitrate (imidazole) is an antifungal or pharmaceutical fungicide used topically to cure athlete's foot, ringworm, tineapityriasis versicolor, jock itch and vaginal thrush. The available products of econazole nitrate present in the market are cream, ointment, lotion, and solution. Adsorption of econazole nitrate is not significant when it is applied to the skin and effective therapy; need a high concentration of active agents to be combined. For this reason, econazole nitrate nanosponges were fabricated by emulsion solvent method and these econazole nitrate nanosponges were loaded in a hydrogel as a topical delivery for sustained release of the drug [24-25].

Itraconazole is also an antifungal drug comes under biopharmaceutical classification system class II and that has a dissolution rate limited and poor bioavailability. So the aim of this study was to increase the solubility of the itraconazole, so that can solve the bioavailability problem. In these nanosponges, if used β-cyclodextrine as cross-linked with carbonate bonds and loaded it with itraconazole than the solubility of itraconazole can be increased.

SYNTHESIS OF NANOSPONGES

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Emulsion solvent diffusion method

In this method, different proportion or amount of ethyl cellulose and polyvinyl alcohol are used to prepare nanosponges. Two phases are used in this method–dispersed and continuous. The dispersed phase consists of ethyl cellulose and the drug, which is then dissolved in 20 ml of dichloromethane and some amount of polyvinyl alcohol (PVA) is added to 150 ml of the continuous phase (aqueous). Then, the mixture is stirred at the speed of 1000 rpm for about 2 h. The product i.e. the nanosponges are collected by filtration. Finally, the product is dried inanoven at a temperature of 400°C [11].

Ultarsound-Assisted synthesis

In this method nanosponges can be obtained by reacting polymers with cross-linkers in the absence of solvent and under sonication. The nanosponges obtained by this method will be spherical and uniform in size (1).

Mix the polymer and the cross-linker in a particular molar ratio in a flask. Place the flask in an ultrasound bath filled with water and heat it to 90°C. Sonicate the mixture for 5hours. Then allow the mixture to cool and break the product roughly. Wash the product with water to remove the non- reacted polymer.

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CHARACTERIZATION OF NANO- SPONGES

Inclusion complexes formed between the drug and nanosponges can be characterized by following methods.

Thermo-analytical methods

Thermo-analytical methods determine whether the drug substance undergoes some change before the thermal degradation of the nanosponge. The change of the drug substance may be melting, evaporation, decomposition, oxidation or polymorphic transition. The change of the drug substance indicates the complex formation. The thermogram obtained by DTA and DSC can be observed for broadening, shifting and appearance of new peaks or disappearance of certain peaks. Changes in the weight loss also can provide supporting evidence for the formation of inclusion complexes (25).

Microscopy studies

Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM) can be used to study the microscopic aspects of the drug, nanosponges and the product (drug/nanosponge complex). The difference in crystallization state of the raw materials and the product seen under electron microscope indicates the formation of the inclusion complexes (11, 25).

Applications of Nanosponges

- Nanosponges based on cyclodextrins can strongly bind organic molecules and remove them from water even at very low concentrations (19). The same concept can be useful for elimination of bitter components from grape fruit juice by selective combination of polymer and cross- linker.
- The microporous hyper cross linked nanosponges have been used in selective separation of inorganic electrolytes by size exclusion chromatography.
- The three dimensional nanosponges will play important role in the fractionalization of peptides for proteomic applications (20).
- Nanosponges can be used as carrier for gases like oxygen and carbon dioxide. These nanosponges could be useful for many biomedical applications. In particular the oxygen-filled nanosponges could supply oxygen to the hypoxic tissues which are present in various deseases (21).
- Nanosponges can selectively soak up biomarkers for the diagnosis. One study concluded that nanosponges can harvest rare cancer marker from blood (22).

CONCLUSION

The nanosponges have the ability to include either lipophilic or hydrophilic drugs and release them in a controlled and predictable manner at the target site. By controlling the ratio of polymer to the cross-linker the particle size and release rate can be modulated. Nanosponges enable the insoluble drugs and protect the active moieties from physicochemical degradation and controlled release. Because of their small size and spherical shape nanosponges can be developed as different dosage forms like parenteral, aerosol, topical, tablets and capsules.

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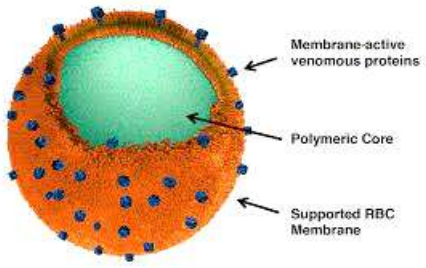

Fig. 1. Nanosponge

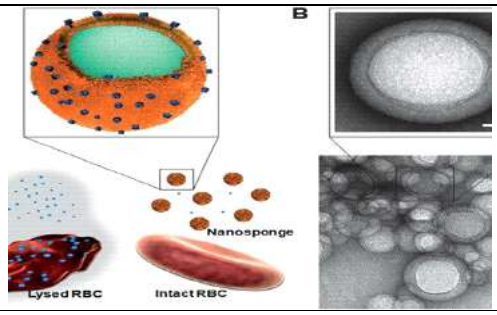

Fig. 2: Structure of a nanosponge showing a cavity for drug loading [3]

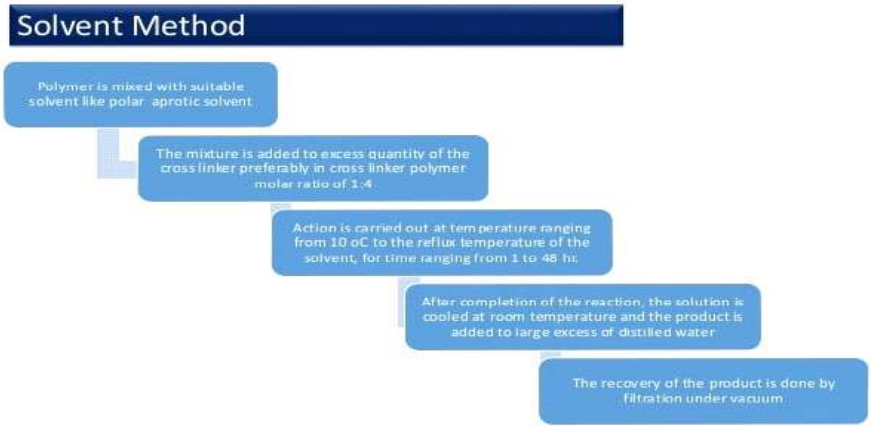

Fig. 3. Solvent Method

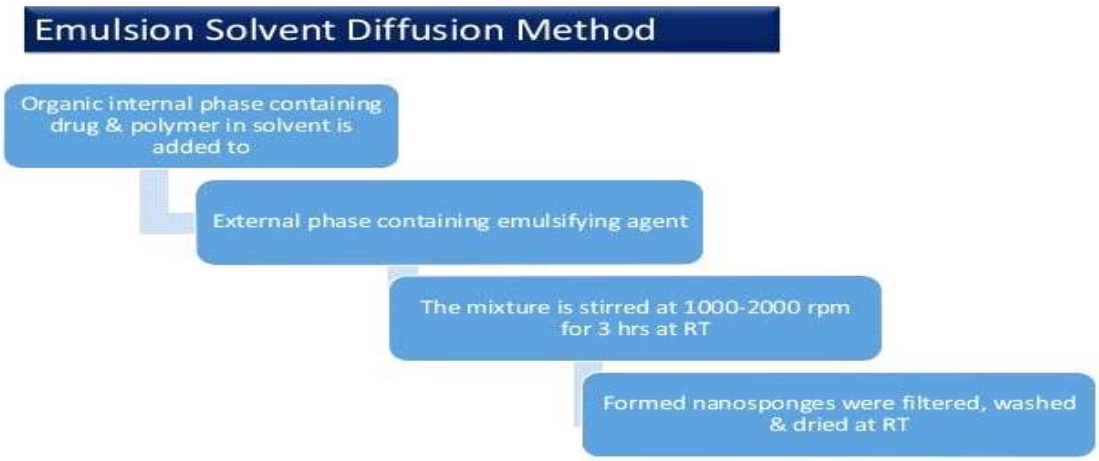

Fig. 4.Emulsion Solvent diffusion Method

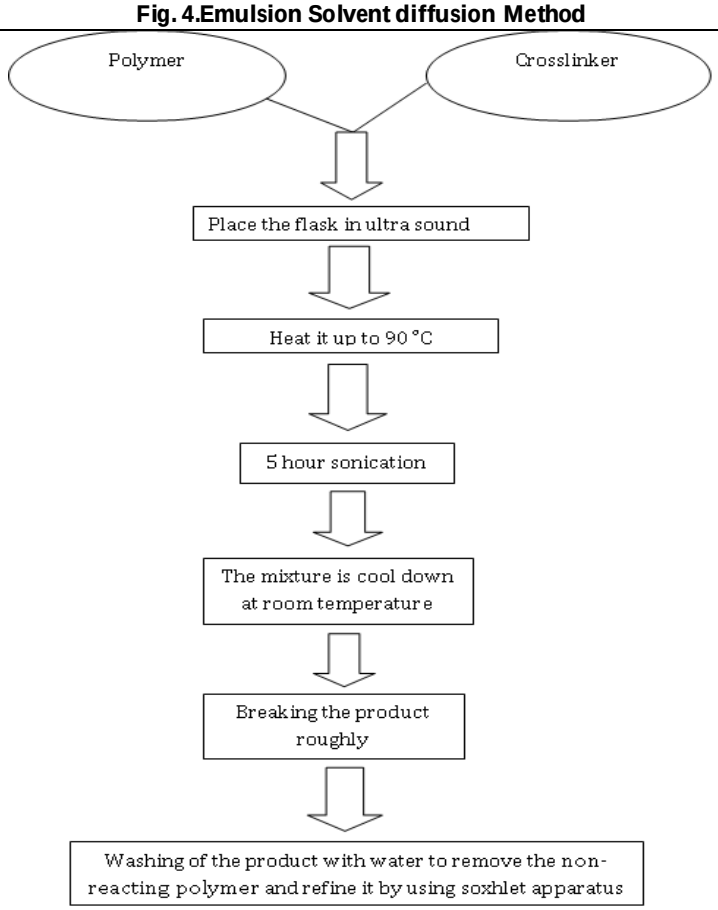

Fig. 5.Ultarsound-Assisted synthesis

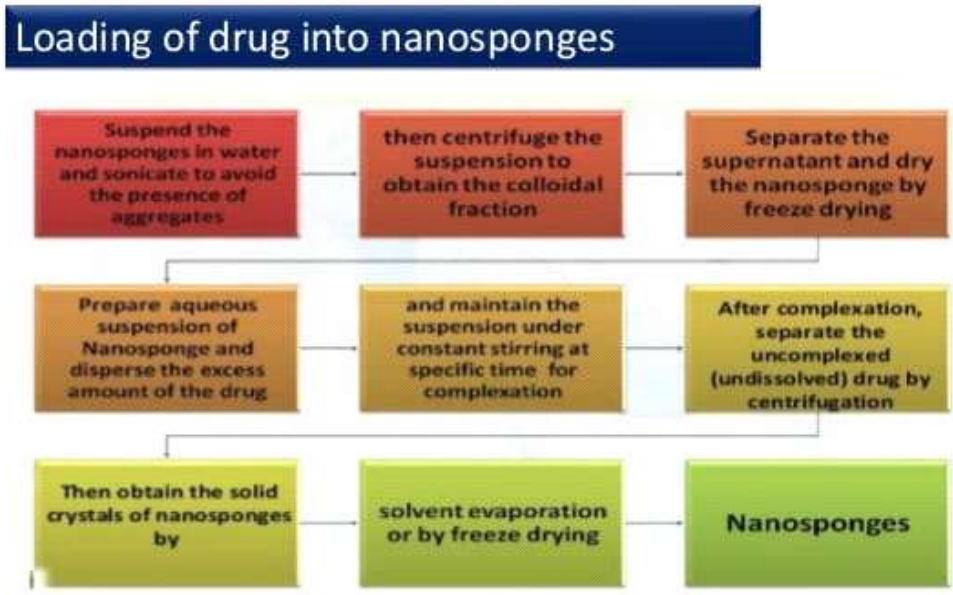

Fig. 6.Loading of drug into nanosponges

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RESEARCH ARTICLE

Micro Algae *Asterarcys* sp. : A Potential Source for Biodiesel Production

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ABSTRACT

The world's economic progress is heavily reliant on fossil fuel supplies, which are restricted not just in terms of availability but also in terms of pollution. Due to the scarcity of fossil fuels, substantial attempts have been made to find alternative biofuels such as bioethanol and biodiesel. The production of biodiesel from micro-algae has several advantages, including higher algal biomass and oil productivities. In this present study, the microalgae *Asterarcys* sp. was isolated from freshwater samples. The predominant strain of *Asterarcys* sp. was screened from the samples. *Asterarcys* sp. (NEIST BT13) was used here as the experimental microalgal strain. The strain shows good growth properties with a specific growth rate of 0.19/day and a doubling time of 3.60 days. The lipid content of the cell after extraction was found to be 20.3% dry cell weight on the 15th day of growth. As a result, Asterarcys sp. has a high fatty acid and lipid content compositions, proving to be a viable strain for biofuel production.

Keywords: Biodiesel, micro-algae, biomass, *Asterarcys* sp., lipid content.

INTRODUCTION

Biodiesel

A biofuel is a fuel produced from the biomass of plants, which includes components from recently deceased organisms as well as metabolic by-products from living species[1,p.163-170]. This biomass can be transformed into biofuels through thermal, chemical, and biological conversion. Biomass fuels have been used throughout human history.Traditional biofuels, also known as "first-generation biofuels," are made from starch, sugar, or vegetable oil, whereas advanced biofuels, also known as "second-generation biofuels," are made from lignocellulosic biomass or woody crops, as well as agricultural wastes or trash.This makes extracting the required advanced biofuel more

difficult, necessitating a variety of physical and chemical treatments before it can be converted to the liquid fuels needed for transportation[2,p.1161-9]. Because of the volatility of oil prices and to reduce reliance on foreign oil, the U.S. government has made renewable energy development a primary priority.President Barack Obama's declaration that "renewable energy is a critical part of policy for the United States" highlights the relative importance of biofuels. Increased biofuel production is now mandated in the United States, generating hundreds of millions of dollars by investing in the fledgling business. The biofuel business provides both energy and basic chemicals, so it serves a dual purpose in the economy [3,p. 197-203].

Only biodiesel and bioethanol, including ethyl tertiary butyl ether (ETBE), account for more than 90% of the biofuel industry on an industrial basis. Alternative substrates such as lignocellulosic have yet to be explored[4]. However, a number of businesses and government-supported research institutes are attempting to develop viable processes. To predict the future of scientific energy innovation, governments and business leaders must first understand how the public assesses the risks and benefits of new technologies such as biofuels.New strategies for successful collaboration between the general public and the research community can be created based on a greater understanding [6,p.36-51].

Biodiesel is a desirable diesel engine fuel because it may be manufactured from any vegetable oil (edible or non-edible), discarded cooking oils, animal fats, and microalgae oils. When used in a diesel engine, it produces less hazardous emissions and is clean energy, renewable, non-toxic, and sustainable alternative to petroleum-based fuels. The attraction of this alternative energy source is that fatty esters acids, also known as biodiesel, have comparable properties to petro-diesel oil, allowing it to be used in compression engines without any modifications. The issue is that biodiesel has viscosities that are roughly twice as high as traditional diesel fuels. As a result, biodiesel esters can be utilized alone or in combination with petro-diesel. These blends are identified by abbreviations such as B20, which stands for a 20 percent biodiesel/80 percent petro-diesel mix. Because of its good balance cost, fewer emissions than petro-diesel, and cold-weather performance, B20 is the most common mix.B100 is a term that refers to 100 percent pure biodiesel[7,p. 1543–1548].These mixes are used to reduce the differences in biodiesel and conventional diesel fuel qualities. Refined vegetable oil is a common lipid source for biodiesel manufacturing. In the European Union, rapeseed and sunflower oils are employed; in tropical countries, palm oil predominates; while in the United States, soybean oil and animal fats are the most common feedstocks. The process for manufacturing biodiesel was invented in the early 1800s and has remained largely unaltered since then. The method of transesterification of triglycerides with alcohol has been utilized in industrial manufacturing to convert vegetable oils into a variety of fatty acid esters. It acts as a catalyst, accelerating the reaction to the right side and resulting in high biodiesel yields. Methyl or ethyl esters are produced, which have qualities that are much more akin to those of regular diesel fuels. Glycerin is the main by-product obtained. Methanol is the most commonly utilized alcohol for biodiesel synthesis due to its low cost and high conversion rates, but other alcohols such as plant-based ethanol, propanol, isopropanol, and butanol can also be used[8,p.430-436].

History of Biodiesel

For the majority of the existence of biodiesel, humanity has relied on renewable energy sources such as windmills, waterwheels, and wood. At the turn of the century, up to 30% of fertile land was cultivated with grains to feed horses and oxen used in transportation..In the 1800s, the technique for producing fuel from biomass feedstock was much the same as it is today. Biodiesel has a more political and economic past than a technological one. Automobiles fuelled by gasoline were first introduced in the early twentieth century. Oil firms were forced to refine so much crude oil in order to supply gasoline that they ended up with a surplus of distillate, which is an excellent diesel fuel that is far less expensive than vegetable oils.Petroleum, on the other hand, has always been a source of concern due to resource depletion, and farmers have constantly looked for new markets for their products.As a result, research into the use of vegetable oils as a fuel has persisted.Meier (1955) was the first to propose using algae as a fuel to manufacture methane gas from the carbohydrate component of cells.Oswald and Golueke (1960) expanded on this concept by presenting a conceptual techno-economic engineering analysis of digesting microalgal biomass produced in huge raceway ponds to generate methane gas. As the cost of conventional fuels began to rise significantly in the

1970s, the potential of using algae as a fuel source resurfaced. Benemann et al. (1978) conducted a more extensive design and engineering examination of this concept, concluding that such systems might produce biogas at prices comparable to expected fossil fuel prices.Farm distillery building construction levied on imported oil, promoting ethanol-fueled appliances (Tweedy, 1917), and research involving ethanol fuel automobiles were all part of the German initiative, which began in 1899. Germany's "Materialbrennereien" program was an early foray into the household and small-scale energy systems. An alcohol motor fuel committee was established in 1914 as part of the British defense research effort (London Times, 1914), assessing supply sources, manufacturing methods, and production prices for alcohol fuel (Fox, 1924).In 1921, the commission found that alcohol would be a more cost-effective fuel than petroleum in tropical and remote areas of the planet (London Times, 1921). Before World War I, the French Agricultural Ministry promoted its ethanol fuel program (in response to rising oil imports from Russia and the United States, as well as rising crop surpluses), resulting in an increase in French ethanol fuel production from 2.7 to 8.3 million gallons from 1900 to 1905. Following the advice of a French committee, Article Six was passed in February 1923, requiring gasoline importers to purchase alcohol for 10% blends from the state alcohol service. Biofuel consumption peaked in 1935 at 406 million liters, accounting for 7% of total fuel consumption, but by 1937, it had dropped to 194 million liters due to poor crop [9,p. 168-179]. As a result of French, German, and British biofuel legislation and research, they have had a global impact.

Importance of biodiesel

Due to the limitations of known petroleum reserves, renewable energy sources will become more appealing. Bio-diesel is the most valued source of renewable energy that can be used in any current diesel engine without modification [4,5,8].

Energy Independence

Given the impact of oil at $ 60 a barrel on the world's poorest countries, which are net importers and rely entirely on imported oil, the question of achieving greater energy independence one day through biofuel development has become one of 'when' rather than 'if,' and now on a near-daily basis. A bio-fuels program is being launched.

Reduced Trade Deficit

Rather than importing old natural resources from other countries, we should use our own living resources to propel our development and strengthen our economies. Instead of hunting for oil in the Middle East, the globe may look for biofuels in the tropics. Producing more biofuels will save foreign cash and lower energy costs, allowing developing countries to invest more in health, education, and other services for their most vulnerable citizens.

Economic Growth

Biofuels, which are made from crops, open up new markets for agricultural products and boost rural development. They have enormous potential for farmers.

Cleaner Air

Biofuels is cleanerto burn than gasoline and diesel.Using biofuels reduces carbon monoxide, particulate matter, and harmful compounds, which produce smog, aggravate respiratory and cardiovascular illness and contribute to thousands of premature deaths each year.

Less Global Warming

Bio-fuels contain carbon taken out of the atmosphere by plants and trees as they grew. Fossil fuels are adding vast amounts of stored carbon dioxide (CO_2) to the atmosphere, where it traps the Earth's heat like a heavy blanket and causes the world to warm. Studies show that biodiesel reduces CO_2 emissions to a considerable extent and almost nearly to zero in some cases.

Sources of Biodiesel

Some of the current commercial biodiesel sources are soybean oil, palm oil, animal fat, and waste cooking oil.Three generations can be distinguished among these sources:

a. Ethanol-based fuels of the first generation, made from sugar fermentation (corn, beet, sugarcane, etc.) and based on vegetable oil (raw oil, biodiesel, and renewable diesel produced from catalytic hydrodeoxygenation)
b. Second Generation- Production of bioethanol or butanol using conventional processes using novel starch, oil, and sugar crops like Jatropha, Cassava, or Miscanthus Lignocellulosic materials (e.g., straw, wood, leaves, grass, etc.) for bioethanol and biobutanol.
c. Biodiesel made from microalgae is the third generation. Microalgae and seaweeds produce bioethanol. Green microalgae and microbes produce biohydrogen.

Microalgae have been dubbed the third-generation biodiesel based on the following classifications. Microalgae can be developed responsibly in the near future and can yield ten times the amount of oil produced by oleaginous plants. Because of its carbon-neutral quality, biodiesel made from microalgae has gained a lot of attention in recent years all around the world. Microalgae create more biofuel than terrestrial plants due to their higher neutral lipid content, and they are the greatest biomass producers. Under photo-oxidative stress and other unfavorable environmental circumstances, they can rapidly accumulate significant amounts of triacylglycerol as a storage lipid. [9,p.168-179].

Importance of microalgae

Global warming is the most severe environmental issue today, which is mostly driven by the widespread use of fossil fuels. The chemical absorption technique can be used to collect CO_2 produced by power plants and industries. Because microalgae can fix CO_2 to produce energy and chemical compounds in the presence of sunshine, they are prospective candidates for utilizing excessive levels of CO_2. Microalgae, in general, are minute organisms that can grow by photosynthesis. Vegetative (asexual) cell division is the primary mode of reproduction in microalgae, while sexual reproduction can occur in many species given the right conditions. Because of their basic cellular structure, their photosynthetic ability is similar to that of land-based plants, and they are immersed in an aqueous environment with easy access to water, CO_2, and nutrients. Microalgae are more efficient than land plants at converting solar energy into biomass. Cyanophyceae (blue-green algae), Chlorophyceae (green algae), Bacillariophyceae (diatoms), and Chrysophyceae are the most common microalgae researched for biodiesel generation (golden-brown algae). Many microalgae can flip between phototrophic and heterotrophic growth modes. Algae cannot synthesis their own food and must rely on glucose or other utilizable carbon sources for carbon metabolism and energy in heterotrophic development. Heterotrophic production is inefficient compared to photosynthetic microalgae production. This is because heterotrophic microbes require renewable organic carbon sources, which are typically supplied by photosynthesis in agricultural plants. Microalgae can be utilised to make a range of environmentally friendly biofuels. Carbohydrates, proteins, and lipids make up the majority of them. Algae are capable of synthesizing[10,p. 391- 397]. Tags are a second-generation feedstock for the synthesis of biofuels. Algal oil's lipid composition, which is being researched in this project, can be converted into biodiesel, carbs into ethanol, and proteins into animal feed or human nutritional supplements. They can also produce methane and fertilizers by anaerobic digestion of the algal biomass. Microalgae also offer the great technical potential for reducing greenhouse gas emissions due to their ability to use carbon dioxide in their photosynthetic efficiency and the ability to grow faster than any other energy crop. They multiply swiftly and can be gathered on a daily basis. Microalgae, on the other hand, must have a high lipid content. Otherwise, achieving economic performance would be difficult. Algae can develop in a variety of environments, including saltwater, freshwater, and even contaminated water.They can grow in the sea, lakes, ponds, even on non-food-producing soil [11].The advantages of microalgae over high plants as a source of biodiesel are numerous [10 p. 391- 397],[11]:

Production of biodiesel

The process of manufacturing biofuel, biodiesel using chemical processes such as transesterification and esterification is known as biodiesel production. Based-catalyzed transesterification is the most prevalent method of synthesis. Microalgae are minute algae that can be found in both freshwater and marine environments. They are single-celled species that can live alone or in groups. Microalgae are capable of photosynthesis and photoautotrophic growth using the greenhouse gas CO_2. They are known to produce over half of the oxygen in the atmosphere. The richness of microalgae is enormous, and they constitute an essentially unexplored resource. *Synechococcus* sp., *Schizochytriummangrovi, Chlorocol cumparinum*, and *Chlorella Vulgaris* have all been identified as possible biodiesel feedstocks.CO_2 concentration, light intensity, temperature, and nutrition are all elements that influence lipid accumulation and cell development in microalgae. Nitrogen and phosphorus are the most vital nutrients, Nitrogen deficit has been linked to a larger level of lipid synthesis in microalgal cells[12,p.124-129].

MATERIALS AND METHODS

Algal strain and culturing and maintenance of microalgae

Asterarcys sp. (NEIST BT13) was used here as the experimental microalgal strain, obtained from the Culture Collection of CSIR-NEIST, Jorhat, Assam. Homogenous cultures of microalgae were grown in a 5 Lts conical flask containing 4 Lts of BG-11 liquid media in a walk-in growth chamber (model no.: SRL-WIPGC-12-A). Culture conditions were maintained at 25 ± 1°C under a 16: 8 light: dark cycle for 15 days. The light intensity of 3500 lux was maintained during the microalgae growth. Even distribution of the cultures was maintained by shaking the flask twice a day. The composition of BG-11 media is shown in table 1.

Microscopic observation

Light microscope

A drop of homogeneous microalgae culture broth was stained with safranin and placed on a glass slide covered with a coverslip. A light microscope was used to exA light microscope was used to examine the slide(Model no. LEICA DM750) at 100X magnification.

Fluorescence microscopy

The intracellular lipid bodies of algal cells were visualized via Nile red (9-diethylamino-5H-benzo[a]-phenoxazine-5-one) staining. One milliliter of green algae (grown for 13 days) was centrifuged at 12,857 ×g for 10 min, and a pellet was re-suspended in 1 ml of 20% DMSO.After 10 minutes of vortexing at ambient temperature, cells were centrifuged at 12,857 ×g for 10 min. Pellet was further suspended in 1 ml of water and vortexed before adding Nile red stain (5µl of 1 mg/ml stock, prepared in isopropanol) and incubated for 5 min in the dark at room temperature. A fluorescent microscope was used to examine stained cells. (Model no. Olympus DP80) using U.V. light with excitation and emission at 530 nm and 575 nm, respectively.

Growth characterization

A growth study on the isolated microalgae was carried out for 15 days in BG-11 media. For monitoring the growth, the optical density (O.D.) was measured at an interval of three days at 685 nm via UV-VIS spectrophotometer (model: Shimadzu UV-2600, North America). For each of the three replicates, the findings were given as means and standard deviations. The specific growth rate (µ) of the isolate was calculated using the formula

$$\mu(day^{-1}) = \frac{(lnC_t - lnC_0)}{(t - t_0)} \quad \text{---------- (1)}$$

where C_t is the O.D. at time t and C_0 is the O.D. at the start of the exponential phase

Doubling time (T_d) was calculated using:

$$T_d\left(days\right) = \frac{ln2}{\mu} \quad \text{----------(2)}$$

Biomass determination

For biomass estimation, 5ml of culture was placed in a pre-weighed glass filter paper. The biomass-containing filter paper was washed twice with distilled water and dried for 24 hours in the oven. The dry weight of the biomass (DCM) was determined gravimetrically and expressed in grams per liter.

Lipid extraction

The lipid concentration was quantified by extracting the lipid using the automated solvent extraction system (Model no. CS03E). The oven-dried algal biomass was homogenized through pulverization in a mortar with a pestle. The pulverized biomass was then placed into cellulose extraction thimbles and located in the extraction unit. The procedure followed to quantify the lipid concentration was boiling for two h, rinsing for 40 min and solvent recovery for 20 min. The extraction temperature for the selected solvent, Hexane (Rankem, India), was 155 °C. Following the oil extraction performed using the extraction system, the extracted lipids were dried at 100 °C for one h, were placed in a vacuum applied desiccator for one h, and were weighed to define the lipid concentration gravimetrically.

RESULTS AND DISCUSSION

Culturing microalgae

The microalgae cultures are grown in the laboratory under controlled conditions in liquid B.G. 11 media and stored in agar slants for the long term. Subculturing of the cultures is done after every fifteen days to maintain the purity of the culture. Figure 1 illustrates the process of cultural growth and maintenance.

Microscopic observation

Light microscopic image

Asterarcys sp. cells ranged from ovoid to coccoid in shape and were spineless. The size of the cell was between 6.8 to 19 μm depending upon the growth condition of the microalgae (Figure 2).

Fluorescence microscopy

The intracellular lipid was observed in the form of the orange-yellow droplet within the cell (Figure 3). The fluorescent microscopic images depicted that the lipid content of the isolated strain was quite high, which was further confirmed by the extraction of the lipid from the cell

Growth characterization study

A growth study on *Asterarcys* sp. was carried out for 15 days in BG-11 media under controlled environmental conditions (25 ^{0}C, 3500 lux, pH 7) (Table 2)(Figure 4). The growth curve (Figure 5) depicted that the logarithmic phase started on the third day from the day of inoculation and continued to grow exponentially till the 15th day showing an optical density of 0.518. A specific growth rate of 0.19/day and a doubling time of 3.60 days were obtained for the studied microalgae. Dry biomass at the end was found to be0.41g/l.

Lipid content of microalgae

Lipid content is inversely proportional to the growth of microalgae which results in decreased biodiesel productivity (Nigam *et al.,* 2011). This calls for a need to explore such isolates which diverge from this principle and make biodiesel production from microalgae an economically viable process in order to study the lipid accumulation in *Asterarcys* sp. NEIST BT-13 15 days old culture of the microalga was dried, and lipid was extracted using the Soxhlet

method. The lipid content of the cell after extraction was found to be 20.3% dry cell weight on the 15th day of growth. This amount was higher than the reported species of *Asterarcys* from Korea (Hong *et al*., 2012).

CONCLUSION AND FUTURE SCOPE

Biofuel production and use have risen dramatically in recent years, but little is known about public opinion on the subject. Because of several constraints, second-generation biofuels are recommended over first-generation biofuels. Before swiftly pushing toward biofuels as a solution for supporting our energy demands, strategic planning, thorough assessment, and transparency in the case of investment are required. Biofuel production must develop sustainable standards, and it must be ensured that the global diversity essential to maintain life on Earth is not harmed by biofuel production.

From the above study, it can be concluded that microalgae *Asterarcys* sp. can be used as a potential source for biodiesel production. The strain shows good growth properties with a specific growth rate of 0.19/day and a doubling time of 3.60 days. The strain also contains a good amount of lipid, suggesting it to be a potent biodiesel-producing source. The study also reports the conversion of the algal oil into fatty acid methyl esters using an acid-catalyzed transesterification reaction. Future work can be done in the field of media optimization to further improve growth. An optimization study would also help in increasing the lipid content of the strain. Work can also be done in the direction of harvesting, as harvesting alone accounts for about 50% of the cost input. These inputs would help in making biodiesel production from the microalgae, *Asterarcys* sp. an economically viable process.With the entire world confronting crises of fossil fuel depletion and significant spikes in petroleum costs, it is critical to look into novel options that can assist reduce oil import dependence and greenhouse gas emissions.

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Table 1: Composition of BG-11 media

Serial no.	Components Macro Nutrients	Amount (g/l)
Macro Nutrients		
1	$NaNO_3$	1500
2	K_2HPO_4	40
3	$MgSO_4.7H_2O$	75
4	$CaCl_2.2H_2O$	36
5	Na_2Co_3	20
6	Citric acid	6
Micro Nutrients		
7	Ammonium ferric citrate	6
8	H_3BO_3	2.86
9	EDTA-Na_2	1
10	$MnCl_2.4H_2O$	1.81
11	$ZnSO_4.7H_2O$	0.22
12	$Na_2MoO_4.2H_2O$	0.39
13	$CuSO_4.5H_2O$	0.08
14	$Co(NO_3)_2.6H_2O$	0.05

Table 2: Growth Data Reading of *Asterarcys* sp

Days	OD1	OD2	AVG OD	ln	log	Specific growth rate	Doubling time
1	0.0135	0.015	0.01425	-4.251	-1.84619		
3	0.0545	0.0481	0.0513	-2.97006	-1.28988		
5	0.1628	0.161	0.1619	-1.82078	-0.79075		
7	0.3032	0.2989	0.30105	-1.20048	-0.52136	0.192690374	3.597207092
9	0.3627	0.3622	0.36245	-1.01487	-0.44075		
11	0.3789	0.3925	0.3857	-0.9527	-0.41375		
13	0.4459	0.4521	0.449	-0.80073	-0.34775		
15	0.4866	0.5494	0.518	-0.65778	-0.28567		

Figure 1: Culturing and maintenance of microalgae culture. A) Microalgae Colony on BG-11 agar plate, B) Homogeneous microalgae culture C) Microalgae slant

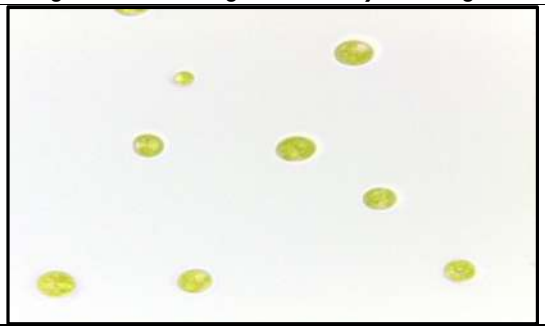

Figure 2: Light microscopic image of microalgae, *Asterarcys* sp. (NEIST BT13)

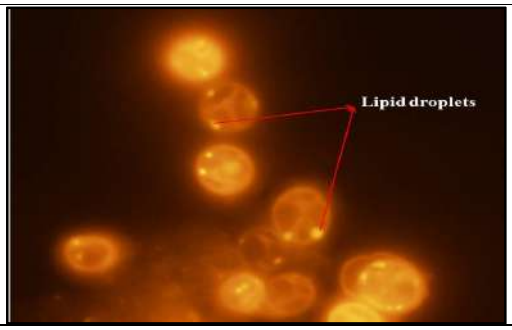

Figure 3: Intracellular lipid droplet visualization using Nile red dye

Figure 4: (a) Growth at day 1, (b) Growth observed at day 8, (c) Growth at day 15

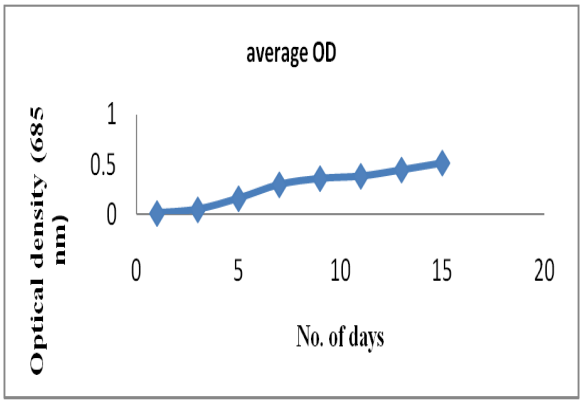

Figure 5: Growth curve for *Asterarcys* sp.

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REVIEW ARTICLE

The GC MS Study of One Ayurvedic Oil, Kottamchukkadi Tailam

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ABSTRACT

The present work deals with Subjecting one Ayurvedic pain relieving oil, Kottamchukkadi thailam to GC MS analysis and to find out the biomolecules present in it. Kottamchukkadi Thailam was bought from a Standard Ayurvedic vendor at Chennai and subjected to GC MS analysis by standard procedures. The GC MS results indicated the presence of some important molecules such as .beta.-Asarone, Nonanoic acid, 1, 3-Benzodioxol-5-ol, n-Hexadecanoic acid, 9-Octadecenoic acid (Z)-, methyl ester, Ethyl methyl sulphone, 2-Hydroxy-4,6-dimethylbenzaldehyde, 15-Hydroxypentadecanoic acid, Z,E-7,11-Hexadecadien-1-yl acetate, Cyclopentadecanone, 2-hydroxy-, Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester, Octadecanoic acid, 2,3-dihydroxypropyl ester, Octanoic acid, 2-tetrahydrofurylmethyl ester, (3-Fluorophenyl) methanol, n-butyl ether, 3-Amino-4-piperonyl-5-

pyrazolone and .gamma.-Sitosterol, which have medicinal roles supporting the pain relieving role of thailam. The roles of some other molecules such as 5-Dodecyne, Cyclohexene, 4-(2-bromoethyl)-, 2-(3-Methylbutyl)-3,5-dimethylpyrazine, 9-Octadecenoic acid, (E)-, 2-(Cyclopent-1-enyl)-thiophene, N-Piperonyl-N-[2-ethoxycarbonylethyl]glycine ethyl ester, 9-Octadecenoic acid, (E)-, Pyrrolidin-2-one, 5-[2-propionylethyl]-, Cyclohexene, 3-methyl-6-(1-methylethyl)-, 7-Oxocholesteryl isocaproate, Stigmastan-3,5-diene, 1,3-Benzodioxole, 5,5'-(tetrahydro-1H,3H-furo[3,4-c]furan-1,4-diyl)bis-, [1S-(1.alpha., 3a.alpha., 4.beta.,6a.alpha.)]-, 1-Hexyl-2-nitrocyclohexane is not reported yet.GC MS results indicated that the medicinal roles of some of the important molecules augur well with the activity of Kottamchukkadi thailam.

Keywords: Ayurvedic; .beta.-Asarone; Ethyl methyl sulphone; GC MS; Kottamchukkadi thailam; Nonanoic acid

INTRODUCTION

Ayurvedic and other traditional medicinal practices need efficacy standardization to prove their validity as safe and effective medicines. GC MS techniqueis one such method to know the presence of molecules present in such medicines. This knowledge can throw some light on the mode and mechanism of actions of the medicine as claimed by these systems of medicines. We have worked on a number of such medicines and the present work is one more report in this direction [1-29]. The present work encompasses the GC study of Kottamchukkadi Thailam, which is an Ayurvedic oil used for the treatment of vata induced disorders such as neuromuscular pains, sciatica, spondylosis, neck pain, arthritis, myalgia, ankle sprain, tennis elbow and relieving numbness pain and stiffness.The oil is used for external applications and in Dhara treatment. This oil is formulated based on Kerala Ayurveda practice, Sahasra Yoga Taila Prakara, 12.There are very few scientific reports on this thailam Patil and Monjkumar, 2017; Kumar and Thakar, 2018) [30-31]. The constituent plants of this oil are mentioned below: 1. *Saussurea lappa,* 2.*Zingiber officinalis,* 3. *Acorus calamus,* 4. *Moringa oliefera,* 5. *Alium sativum,* 6. *Capparis sepiaria,* 7. *Brassica juncea,* 8. *Pluchea lanceolata.* 21 grams of each plant is made into paste in 768 ml of seasum oil and added with 768 ml of Curd. This mixture is added to 3.072 liters of Tamarind (*Tamarindus indica*) juice and heated in slow flame till the water evaporate and oil is obtained. Some of the manufacturers of this oil are Kottakkalarya Vaidyasala, AVP and AVN.

RESULTS AND DISCUSSION

Figure 1 shows the GC MS profile graph of Kottamachukkadi Thailam. Table1 indicates the retentions time, type of possible compound, peak area, peak height, molecular mass, and the medicinal roles of each compound as shown in the GC MS profile of Kottamachukkadi Thailam. The identification of metabolites was accomplished by comparison of retention time and fragmentation pattern with mass spectra in the NIST spectral library stored in the computer software (version 1.10 beta, Shimadzu) of the GC-MS along with the possible pharmaceutical roles of each bio molecule as per Dr. Duke's Phytochemical and ethnobotanical data base (National Agriculture Library, USA) and others as shown in Table 1. [32] among the compounds present, .beta.-Asarone has been attributed to have functions such as 17-beta-hydroxysteroid dehydrogenase inhibitor, Antiamyloid-Beta, Anti TGF-Beta, Beta-2-Receptor-Agonist, Beta-Adrenergic receptor blocker, Beta Galactosidase inhibitor, Beta-Glucuronidase inhibitor etc. 17-beta hydroxylsteroid dehydrogenase enzymes helps in the formation of steroid hormones, both estrogens and androgens, from their precursors in different cells and tissues. Steroids function as anti-inflammatory and anti-allergic by acting on the immune system and often used for extreme cases such as asthma and arthritis. The presence of .beta.-Asarone inthis oil works as an inhibitor of 17-beta hydroxyl-steroid dehydrogenase thus reducing or stopping the formation of steroids, thus saving the immune system of adverse side effects of steroids. The same function could be attributed

to .beta Asarone as Beta blocker and as anti TGF Beta role, which could help in maintaining the homeostasis of the skin cells thus helping in early remedy of the skin diseases.As anti a*myloid beta* ($A\beta$ or Abeta), this molecule must be playing a role to save the brain from developing amyloid plaquesthus protecting from the onset of Alzeimer's disease. Anti TGF Beta role, which could help in maintaining the homeostasis of the skin cells thus helping in early remedy of the skin diseases(Gramont*et al,*2016).[33]Beta blockers, or, beta-adrenergic blockers reduce effect of hormone epinephrine leading to slowing down of heart rate and reducing the blood pressure. Thus .beta.-Asarone could reduce the Blood pressure and somehow helps maintain homeostasis. B-galactosidase breaks down galactosides releasing glucose in the blood. By functioning as inhibitors of B galactosase enzyme, the skin cells will have less free glucose, which could starve the infections and thus leading to early cure. .gamma.-Sitosterolis a molecule which has a PPAR-Gamma-Antagonist role. This role is similar to NSAID for reducing the pain and inflammation.n-Hexadecanoic acid, Cyclopentadecanone, 2-hydroxy-, Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester, (3-Fluorophenyl) methanol and n-butyl ether have medicinal role, such as Arylamine *N*-acetyltransferases inhibitor.

Arylamine *N*-acetyltransferases (NAT) are phase II xenobiotic-metabolizing enzymes (XME) which catalyze the transfer of an acetyl group from acetyl-coenzyme A (AcCoa) to the nitrogen or oxygen group of aromatic amine chemicals. Thus, these enzymes are key players in the detoxification and/or bioactivation of several aromatic amine drugs and carcinogens (Hein *et al*, 2000; Sim*et al,*2012).[34, 35]This inhibitory role of the molecules present in this oil must be arresting the conversion of xenobiotics present in the body, thus saving the system form allergies and even cancer. Similarly, another molecule, namely, Z,E-7,11-Hexadecadien-1-yl acetate has been reported to have anticancer and antitumor properties.

CONCLUSION

From the above discussion it is clear that the molecules, as shown by the GC MS profile of Kottamchukkadi thailam, do have some very crucial roles towards its claim as a potent medicine for the diseases ascribed to it.

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Table 1. Indicates the retentions time, types of possible compound, peak area, peak height, molecular mass and the possible medicinal roles of each compound as shown in the GC MS profile of Kottamchukkadi Thailam.

Sl. No.	Retention Time	Name of Molecule	Peak Area	Peak Height	Mol.Mass	Medicinal Role
1	6.47	Nonanoic acid	35219674	4292038	158.1	Acidifier, Acidulant, Arachidonic acid inhibitor, increases aromatic amino acid decarboxylase activity, inhibit production of uric acid.
2	6.858	1,3-Benzodioxol-5-ol	16972136	5074424	138	Oligosaccharide provider
3	9.395	.beta.-Asarone	37465566	9099303	208.1	17-beta-hydroxysteroid dehydrogenase inhibitor, Antiamyloid-Beta, Anti TGF-Beta, Beta-2-Receptor-Agonist, Beta-Adrenergic receptor blocker, Beta Galactosidase inhibitor, Beta-Glucuronidase inhibitor
4	11.876	n-Hexadecanoic acid	720405760	10921863	256.2	Acidifier, Acidulant, Arachidonic acid inhibitor, increases aromatic amino acid decarboxylase activity, inhibit production of uric acid, Anaphylactic, Anti-tumor, Aryl amine N acetyl transferase inhibitor, decreases nor epinephrine production, down regulates uptake of nuclear and cytosol androgen, GABA-nergic,

						Increase NK cell activity, Inhibits tumor necrosis factor, myo-neuron stimulator
5	12.81	5-Dodecyne	26523014	2171050	166.2	Not Known
6	12.868	9-Octadecenoic acid (Z)-, methyl ester	35052176	1878605	296.3	Increases Zinc bioavailability, provides zinc, Catechol o methyl Transferase inhibitor, methyl donar, methyl guanidine inhibitor, Arachidonic acid inhibitor, increases aromatic amino acid decarboxylase activity, inhibits production of uric acid
7	13.287	Ethyl methyl sulphone	155036626	10205781	108	Catechol o methyl Transferase inhibitor, methyl donar, methyl guanidine inhibitor
8	13.302	Cyclohexene, 4-(2-bromoethyl)	1029130857	11123206	188	Not known
9	13.325	1,2-Benzisothiazole-3-ethanol, acetate (ester)	19575724	6938004	221.1	Ethanol Absorption inhibitor, Ethanolytic
10	13.342	2-(3-Methylbutyl)-3,5-dimethylpyrazine	168035390	9670057	178.1	Not known
11	13.36	9-Octadecenoic acid, (E)-	1503171327	10069974	282.3	Not known
12	13.475	2-Hydroxy-4,6-dimethylbenzaldehyde	32634318	3746441	150.1	17-beta-hydroxysteroid dehydrogenase inhibitor, Aryl-Hydrocarbon Hydroxylase inhibitor, Testosterone Hydroxylase inducer
13	13.482	2-(Cyclopent-1-enyl)-thiophene	22751181	3746441	150.1	Not known
14	14.526	15-Hydroxypentadecanoic acid	209334401	9902640	258.2	Arachidonic acid inhibitor, increase aromatic amino acid decarboxylase activity, inhibits production of uric acid
15	14.535	Succinic acid, di(5-fluoro-2-nitrophenyl) ester	17682502	3461001	396	Succinic dehydrogenase inhibitor, Antidote, Coronary dilator
16	15.954	Z,E-7,11-Hexadecadien-1-yl acetate	309901083	9192562	280.2	Increases zinc bioavailability, anticancer, antidote, antitumor, Cytochrome-P450-2E1-Inhibitor, Decreases C-Teleopeptide Excretion, Decreases Deoxypyridinoline Excretion, DecreasesEndothilial Leukocyte Adhesion, Decreases Epinephrine Production, Decreases Oxalate Excretion
17	15.997	Cyclopentadecanone, 2-hydroxy	446402642	10154370	249.2	17-beta-hydroxysteroid dehydrogenase inhibitor, Aryl-

						Hydrocarbon Hydroxylase inhibitor, Testosterone Hydroxylase inducer
18	16.242	Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester	323555797	9971609	330.3	17-beta-hydroxysteroid dehydrogenase inhibitor, Aryl-Hydrocarbon Hydroxylase inhibitor, Testosterone Hydroxylase inducer, Arachidonic acid inhibitor, increases aromatic amino acid decarboxylase activity, inhibits production of uric acid
19	17.627	N-Piperonyl-N-[2-ethoxycarbonylethyl] glycine ethyl ester	47666891	4502462	337.2	Not known
20	17.648	9-Octadecenoic acid, (E)-	1097728372	10053001	282.3	Not known
21	17.811	Octadecanoic acid, 2,3-dihydroxypropyl ester	42963119	3651341	358.3	Acidifier, Acidulant, Arachidonic acid inhibitor, increases aromatic amino acid decarboxylase activity, inhibit production of uric acid.
22	17.82	Pyrrolidin-2-one, 5-[2-propionylethyl]-	24349071	3651341	169.1	Not known
23	18.344	Octanoic acid, 2-tetrahydrofurylmethyl ester	31521338	3301532	228.2	Acidifier, Acidulant, Arachidonic acid inhibitor, increases aromatic amino acid decarboxylase activity, inhibits production of uric acid.
24	19.037	Cyclohexene, 3-methyl-6-(1-methylethyl)-	24056171	1447912	138.1	Not known
25	19.059	(3-Fluorophenyl) methanol, n-butyl ether	23519855	3848737	182.1	Anaphylactic, Antitumor, Arylamine-N-Acetyl-transferase-inhibitor, Decreases Norepinephrine production, Down regulates reuptake of nuclear and cytosol androgen, GABA-nergic, Increases NK cell activity, inhibits production of tumor necrosis factor, Myoneuron stimulator, N-cholinolytic, NADH-Oxidase-Inhibitor, NADH-Ubiquinone-Oxidoreductase-Inhibitor
26	19.781	7-Oxocholesteryl isocaproate	16705437	883927	498.4	Not known
27	20.383	Stigmastan-3,5-diene	34369750	1508635	396.4	Not known
28	20.708	1,3-Benzodioxole, 5,5'-(tetrahydro-1H,3H-furo[3,4-c]furan1,4-diyl)bis-, [1S-	211418139	10933223	354.1	Not known

		(1.alpha.,3a.alpha.,4.beta.,6a.alpha.)]-				
29	21.079	3-Amino-4-piperonyl-5-pyrazolone	45722669	9693104	233.1	Increases Aromatic amino acid decarboxylase activity
30	21.77	.gamma.-Sitosterol	41944617	974261	414.1	PPAR-Gamma-Antagonist
31	23.831	1-Hexyl-2-nitrocyclohexane	35877390	1641992	213.2	Not known

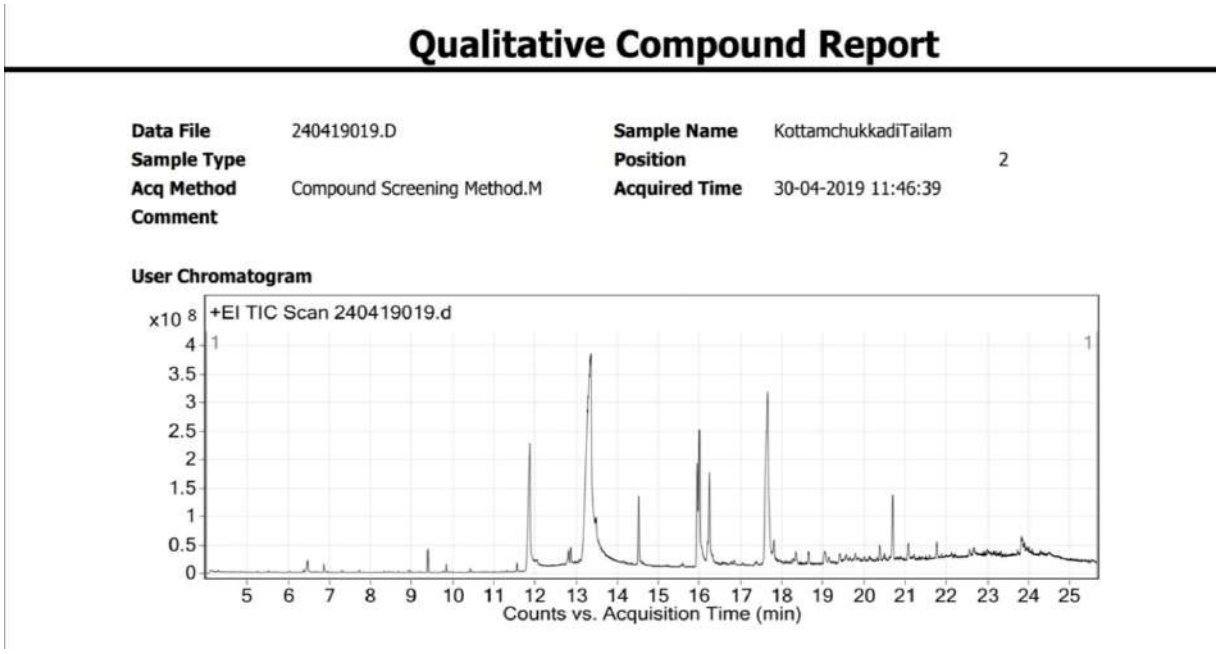

Figure 1. Indicates the GC MS graph profile of Kottamchukkadi thialam

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RESEARCH ARTICLE

Wireless Sensor Networks in Modern Agriculture (WSN)

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ABSTRACT

Agriculture is India's backbone, and agriculture employs almost 70% of the country's population. Agriculture's yield needs be expanded swiftly in order to meet the world's population's food demands. Wireless Sensor Networks (WSN) are now being used to solve a variety of real-time problems.WSN is important in a variety of fields, including transportation, medical, military, mobile phones, and household appliances. Agriculture is a vital source of food for all living beings. However, various environmental changes are affecting agriculture crops nowadays. In order to overcome this, WSN plays a vital role in agriculture.WSN is used in agriculture for monitoring, temperature measurement, irrigation system monitoring, water supply monitoring, and so on.WSN assists the farmer in producing a large quantity of crop while lowering the yield cost. Climate change, environmental change, and natural disasters all have an impact on agriculture. Soil and water management can be done with WSN. Because wireless sensors are employed, the implementation costs are very inexpensive. Wireless sensor nodes are employed to monitor the crops in this paper. Sensors can be used to detect temperature, humidity, and other types of theft. This aids in increasing agricultural productivity. The computerised procedure reduces human work and encourages farmers to develop their farmland.GPS can be used to convey the location of the farmland. Sensors, Wi-Fi, cameras, and other equipment are employed to make agriculture as smart as possible. All of the obtained data is saved in memory or on the cloud.

Keywords: -Wireless Sensor Network, Access Point, Sensor Nodes, Smart Phone, Web Server (WSN)

INTRODUCTION

Farmers can use wireless sensor networks to help them transition from traditional to modern agriculture.WSN assists farmers in a variety of ways. Wireless Sensor Networks collect data from scattered sensors and send it through wireless networks. Micro sensors are utilised in WSN, and the sensors use the global positioning system (GPS) to determine the actual location. It is mostly used to track environmental changes such as climate shifts, temperature, humidity, and soil testing. Sensor networks are small, inexpensive, and can even be employed in rural locations. There are three types of topologies used in wireless sensor networks. They are star, cluster tree, and mesh, and connections can be made utilising these topologies. Battery, radio, microcontroller, analogue circuit, and sensor interface are some of the components used by WSN. Crops must be developed at a minimal cost and in a short amount of time, allowing the farmer to earn a large profit. Human labour in agriculture can be minimised by using WSN. Agriculture is a necessity for all humans in order to obtain food and other raw materials. Agriculture is the primary source of economic growth. Agriculture employs a large number of ignorant people. Regrettably, farmers still rely on outdated methods, which restrict growing yield.

But when the automatic system is implemented in agriculture, it used to increase the yield of crop. The most of the paper use Wireless sensor network to collect the data of farm land using sensors and sent it to server using some wireless protocols. All the collected information provides data and it used to increase the yield of crop. The collected data present in server is not enough to increase the growth of crop. There are some other factors which affect the growth of crop. The wild animals and birds can affect the crop it can't be reduced. There are some other factors like insects and pests can affect the agriculture. Some people involves in theft when the growth of crop reached for harvesting. The storage of harvested crops is very difficult for farmers. In this paper the soil moisture content is measured. The infected plants is measured using bio sensor and the result is send to farmer's mobile phone. The role of sensor is very important and all the devices are connected to internet. The GPS is used to share the location of farm land with farmer and also with agriculture officer. Here the temperature, humidity sensor is used to measure the temperature and humidity of the farm land is measured.

Literature Survey

A Novel Approach for Precision Agriculture Using Wireless Sensor Network [1] In this paper wireless sensors are used to monitor the crops found on the agriculture lands. Sensor networks are used to measure the water level, temperature, humidity, pesticides and so on [2] [3]. Wireless sensors are very cheap, small. Here few sensors are developed for monitoring the agriculture lands. Using these sensors the time and effort for growing the crops can be reduced and the productivity can be increased. WSN use different types of topologies like bus, star, grid and ring. In star topology all the nodes cannot communicate directly [4]. Compare to other topologies ring network is better because for every node only two neighbours are present for communication. The messages can be transmitted in both clockwise and also in anticlockwise direction. 5] [6] In this paper wireless sensor network is also called as Zigbee Network. In this sensors are called as nodes and those nodes are embedded with other sensors. It used to measure temperature and humidity. Nodes monitor the environment and forward the information to router. Router forward the data's to co-coordinator which is connected to internet [7]. Finally all the collected data's are stored in database for processing. Here computers and mobile application are used to monitor the greenhouse [8]. Smart phone android applications are designed and connected to internet. Application is connected to web server and can monitor the crops without the help of human. Agriculture Field Monitoring using Wireless Sensor Networks to Improving Crop Production [9].

In this paper WSN are used in all kinds of crops for monitoring as well as for delivering the water, fertilizer and also for other uses. Data are not collected frequently from the crops because frequent collection does not provide any useful information and it provide heavy burden to sensors [10] [11]. Hour based data collection can be done. This helps the farmer to grow the crop and earn high yield with low cost . Smart Precision based Agriculture using

Sensors [12] [13] In this paper sensors are used for monitoring the soil moisture, humidity level and send the data through network. It reduces the human effort and the crop can be yield with low cost. In the implementation raspberry pi is used and it is connected to 5V power supply. The soil moisture sensor and humidity sensor are used for measuring soil and humidity. Using serial communication data are transmitted in the form of 0's and 1's [14] [15]. Where 0 indicate the motor is turned on. Permissible level get reach the notification is send to user mobile. Motor can be turned using smart phones. Each and every 1 minute moisture values are monitored using moisture sensor. Required level is reached motor gets off automatically. 16] In this paper the mobile robot sensor is used as node 1. It is used to control the water pumps automatically. The level of water content is low the pump gets ON automatically or the level of water content in a land is high the pump gets OFF automatically. In node 2 some sensors like light sensor, motion detector, humidity sensor, room heater, temperature sensor are used in raspberry pi. The temperature sensor used to measure the level of temperature in farm land. In node 3 the moisture sensor is used to measure the soil content in farm land. The transmitted data is send to node 2 and it is send to microcontroller. The data is used to control the water pumps. Raspberry pi is a small size computer.

used for computing and network. All the data is send to farmer mobile phone. The data is send to base station through GPS (Global Positioning System). The microcontroller is used to transmit the data to raspberry pi. [17] In this paper to produce the crop with high yield and to reduce the human effort. In this paper some sensors are used to measure the crop land. Sensors like Temperature Sensor, Moisture Sensor, Pressure Sensor and Humidity Sensor are used in farm land. The change in Temperature in the form land used to reduce the nutrient content in form land. Moisture Sensor works on the principle of electrical conductivity. The Moisture content is one of the important factor of crop growth. The Pressure Sensor connected to microcontroller to regulate the water flow. The Humidity Sensor used to measure Humidity level in air.

Sensor

The temperature sensor used to measure the amount of temperature in the farm land. The temperature like coldness or heat can be measured using temperature sensor. There are two types of temperature sensors are available. The contact temperature sensor and non- contact temperature sensor used to measure the temperature. The humidity sensor is used to measure the level of humidity in air. It measure both moisture and air content. The humidity sensor is also called as dew sensor. There are two electrical conductors conduct the electric field between them. The sensors is composed between two metal plates and conduct the polymer firm between two electrical conductors. It used in farm lands to measure the water content of soil. The soil moisture sensor is very simple to measure the volumetric water content in farm land. It helps the farmer irrigation system more efficiently. This soil moisture sensor is used in urban and suburban areas. It is also used in horticulture, climate research and also in environmental science. The voltage used by soil moisture sensor is 5V and the current used by it is < 20mA. The temperature used by soil moisture sensor is 10-30 degree C.

The bio sensor is used to measure the microorganism, antibodies and so on. It use the components like bio element, transducer, amplifier, processor and display. Here it used to measure the infection of plants. The level of defect is measured and the process is done. The level of infection is less the notification message is send to mobile phone of farmer. The level of infection is high the message is send to mobile phone of farmer as well as to the agriculture officer of particular village. The agriculture officer receive the message with location of the farm land. The location is determined by GPS and send to officer

Proposed System

Instead of using traditional agriculture modern agriculture can be done by farmers in this modern word. In this paper the wireless sensor networks are used to monitor the crops. The farmer can measure the water level, humidity, moisture content and also the diseases affected in the crops. The sensors collect the related information and store it on the webserver. Immediately sends the related data to two members using already registered phone numbers. One is farmer and another one is nearby agriculture specialist. The agriculture specialist communicates with the farmer

directly and suggests the pesticides. Both can monitor the crops using their smart phones. The information is received through their smart phones. The android Smartphone is used by all kind of people. The smart phone consists of multiple applications (apps). For modern agriculture the special kind of app is designed to monitor the agriculture land. These applications can be accessed through internet, which is connected to web server. The farmer can monitor the land from anywhere. The agriculture specialist can also monitor the land from anywhere and send the solution to the farmer through the application itself. Many farmers are connected to the application; they can also give their solution to the infections on the crop

Future Scope

The smart farm helps the farmer to yield high profit by growing the crop without infection and at exact soil moisture content. Due to automatic process it reduce the human effort and view the growth of crop through smart phone. The wireless communication reduce the cost of implementation. In future this is implemented for large area of land. The internet connectivity is required at all the time to communicate the data to farmer. The predefined prediction of weather condition helps the farmer to cultivate the crop based on weather condition.

CONCLUSION

Agriculture can be done using a variety of current technologies in today's world.WSN are utilised in this case to produce a high-yielding, low-cost crop. Nowadays, humans are not active in agriculture. Wireless sensor networks are utilised to reduce human effort. Sensor nodes capture data at this location and communicate it to farmers and agriculture specialists. Data is delivered to smart phones with the help of some additional hardware and software. Mobile phones can be used by the farmer at any time and from any location. This application might include a large number of farmers as well as specialists. This is more appropriate for countries that rely heavily on agriculture, such as India.

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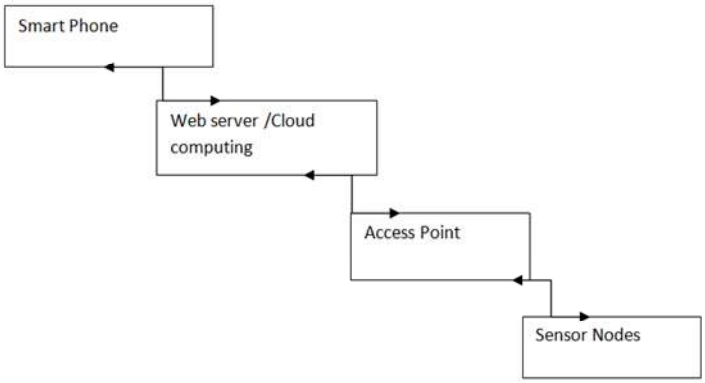

Fig.1. Architecture of Proposed System

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REVIEW ARTICLE

A Review on Modern Aspects of Prodrug

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ABSTRACT

The term 'prodrug' is utilized to portray intensifies that should go through substance change inside the body prior to applying their pharmacological or helpful activity. The fundamental point of prodrug configuration is to veil bothersome medication properties, like low solvency in water or lipid layers, low objective selectivity, compound flimsiness, unfortunate taste, aggravation or torment after nearby organization, pre-foundational digestion poisonousness. While it includes some essential goals of drug, pharmacokinetic, pharmacodynamic approaches. These get arranged dependent on their linkages and adjustment as transporter connected, antecedent, and on its remedial classifications., and so forth These likewise include the presence of specific rules dependent on its transporter linkages, amino acids, lipids, polysaccharides, alcohols, amines, polymers., and so on prodrugs include further developing solvency, improving porousness, expanded lipophilicity, and furthermore quiet consistence. It goes through factors choice of parent medication and distinguishing proof of advances. These might uncover the clinical uses of prodrug and current methodologies of item.

Keywords: Prodrug, lipophilicity, Chloramphenicol, drug action, absorption

INTRODUCTION

During the most recent twenty years, there has been a consistent improvement in the physicochemical, biopharmaceutical, and additionally pharmacokinetic properties of pharmacologically dynamic mixtures by the execution of a prodrug methodology. It is assessed that presently about 10% of overall showcased medications can be named prodrugs. Additionally, in 2008, 33% of all endorsed little atomic weight drugs were prodrugs[1]. The primary compound satisfying the old style standards of a prodrug was acetanilide, presented (under the name of Antifebrin) into the clinical practices an antipyretic specialist. Acetanilide and phenacetin were not initially planned as prodrugs, however their prodrug still up in the air later on. The term 'prodrug' is utilized to depict intensifies that

should go through substance change inside the body prior to applying their pharmacological or restorative activity. The term 'prodrug' or 'master specialist' was first utilized by Albert who recommended that this methodology could be utilized to modify the properties of medications, briefly, to expand their convenience, or to diminish related toxicity[2].

Concepts of Prodrug

The fundamental point of prodrug configuration is to veil unfortunate medication properties, like low dissolvability in water or lipid films, low objective selectivity, compound unsteadiness, bothersome taste, aggravation or torment after nearby organization, pre-foundational digestion, and toxicity[3,4]. Rationally, the utilization of prodrugs is to upgrade the retention, dispersion, digestion, discharge, and undesirable poisonousness (purported ADMET properties) of the parent drugs. The dynamic medication is delivered from its latent structure previously, during, or after retention of the prodrug. A few medications are delivered solely after arriving at the objectives of their actions[5].

Classification

There are two main classes of prodrugs

A. Carrier-linked prodrugs

B. Bio-precursor prodrugs.

A. Carrier-Linked Prodrugs[6,7]

In the transporter connected prodrugs, the dynamic atom (the medication) is briefly connected to a transporter (otherwise called a supportive of moiety) through a bio-reversible covalent linkage. Once in the body, the transporter connected prodrug goes through biotransformation, delivering the parent drug and the transporter. In a perfect world, the transporter ought to be nonimmunogenic, simple to integrate for a minimal price, stable under the states of prodrug organization, and go through biodegradation to nonactive metabolites.

Instances of co-drug incorporate,

- ✓ Sulfapyridine – 5-aminosalicylic corrosive,
- ✓ Indomethacin – paracetamol,
- ✓ L-DOPA – entacapone,
- ✓ gabapentin – pregabalin,

Bio-Precursors[8,9]

Bio-antecedents don't contain a favorable to moiety however result from a sub-atomic adjustment of the dynamic compound itself. The bio-antecedent prodrug is changed metabolically or synthetically by,

- ✓ Hydration (e.g., lactones like a few statins),
- ✓ Oxidation (e.g., dexpanthenol, nabumetone) or
- ✓ Reduction (e.g., sulindac, platinum(IV) edifices) to the dynamic specialist

Criteria for Carriers

In an optimal circumstance, the transporter ought not have inborn poisonousness. The transporter ought to likewise be non antigenic and non-immunogenic, and ought not amass in the body[10]. All things being equal, the transporter ought to have acceptable utilitarian gatherings for satisfactory stacking limit and medication connection. It ought to likewise be somewhat simple to deliver for a minimal price. A transporter should stay stable under prodrug organization conditions, synthetic control, and autoclaving. It ought to go through biodegradation to latent metabolites.

Aminoacids as prodrug carriers

Amino acids do have a demonstrated record of being effectively utilized as supportive of moieties in the amalgamation of prodrugs[11]. Lately, a hot field concerning drug conveyance research has focused on

creating amino corrosive prodrugs for various dynamic carrier designated conveyance objectives. Most amino corrosive prodrugs are either esters or amides, in which amine or carboxylic gathering of amino corrosive is joined to hydroxyl, amine or carboxyl gathering of medication moiety. Advantages of amino acids as supportive of moieties incorporate huge underlying variety; they are typical dietary constituents and are nontoxic in moderate portions when contrasted with other favorable to moieties; a wide scope of utilitarian gatherings like hydroxyl, amine, or carboxylic corrosive gathering, which can be connected to parent drug; grounded prodrug science; business accessibility; less security concerns; substrates for various gastrointestinal inundation carriers.

Polysaccharides as prodrug carriers

Polysaccharides are utilized as favorable to moieties explicitly for colon focusing on drug conveyance. Different polysaccharides, for example, cyclodextrin, dextran, gelatin, chitosan, and chondroitin are formed with drugs[12]. Chondroitin sulfate, a copolymer of D-glucuronic corrosive and sulfated N acetyl D-galactosa mine, is a significant underlying part in connective tissue and ligament. It tends to be utilized as a decent contender for colon-designated drug transporters.

Alcohols as prodrug carriers

Esters rule research because of their ideal qualities that show adequate synthetic soundness in vitro and their capacity to work as esterase substrates for in vivo regeneration[13]. Alcohols structure ester bonds with carboxylic gatherings of medication moiety.

Amines as Prodrug Carriers

For the combination of amide prodrugs, different amines like propylamine, dimethylamine, cyclohexylamine, 2-amino ethyl amine, 2-hydroxyl ethylamine, ethylenediamine, benzathine, and cysteamine are utilized as transporters. These structure amide bonds with carboxylic gatherings of medication moiety[14].

Role of Prodrug in Pharmacokinetics

Prodrugs are substances that are regulated in a latent structure and afterward utilized in the body into the dynamic drug[15]. This digestion happens either by enzymatic or synthetic change. Prodrugs assume a part in working on the unfortunate properties of investigational or promoted drugs and regularly center around the streamlining of the retention, dispersion, digestion, and discharge (ADME) properties of the dynamic mixtures. Numerous prodrugs are intended to further develop drug conveyance and oral bioavailability of medications that show helpless assimilation from the gastrointestinal plot.

i) Improving Solubility Using Prodrugs

Helpless solvency is a significant issue in drug disclosure and prodrugs are viewed as an elective methodology where the utilization of excipients or salt arrangement has not been effective. The presentation of phosphates, amino corrosive esters, or amides moieties into the atom is generally used to improve dissolvability in the gastrointestinal tract[16].

ii) Enhancing Permeability Using Prodrugs:

Further developing porousness using prodrugs can be accomplished in several distinct ways. Initially, expanding the lipophilicity of the particle by covering polar utilitarian gatherings and hydrogen bonds with ester or amide linkers is a typical way to deal with address helpless latent porousness. An illustration of this kind of prodrug is oseltamivir which is an ethyl ester prodrug and goes through quick transformation via carboxylesterase to the parent drug.

Advantages of Prodrug : Prodrug adjustments can eliminate undesirable medication properties or they can add or hold beneficial medication properties as far as bioavailability, viability, or safety[17]. There are many benefits of prodrugs. Some particular advantages of prodrug improvement include:

Increased Solubility

Many medications are ineffectively invested in a fluid climate, which can prompt low oral bioavailability. The expansion of a polar particle (e.g., certain esters and amide gatherings) can assist a medication with being consumed, and accordingly permit it to arrive at the objective tissue in a sufficiently high focus to be successful.

Increased Lipophilicity

Lipophilicity is additionally a significant property for drug particles since movement through lipophilic films in the body is fundamental for retention and distribution. For instance, the expansion of a lipophilic moiety to a medication can assist it with going through the blood-mind boundary if the medication needs to arrive at the cerebrum to be compelling.

Selective Targeting to Site

Preferably, a medication would discover its direction to the proper objective site without investing a lot of energy somewhere else in the body. To assist with accomplishing this, prodrugs can be intended to be delivered in explicit organs or tissues where they will be the most viable. Various strategies might be utilized to accomplish particular focusing on, for example, planning a prodrug to target explicit carriers or actuating compounds in the body.

Protection from Rapid Elimination

Proteins in the body can quickly utilize a few medications, making them be killed before a satisfactory helpful impact has taken place. For instance, digestion through catalysts in the stomach related framework can prompt sped up drug freedom. A more drawn out term of activity can be accomplished through prodrugs that forestall fast digestion, in this manner expanding the half-existence of a parent compound.

Benefits of Prodrug

Prodrug modifications can remove unwanted drug properties or they can add or retain advantageous drug properties in terms of bioavailability, efficacy, or safety. There are many advantages of prodrugs. Some specific benefits of prodrug development include:

Increased Solubility

Many drugs are poorly absorbed in an aqueous environment, which can lead to low oral bioavailability. The addition of a polar molecule (e.g., certain esters and amide groups) can help a drug be better absorbed, and therefore allow it to reach the target tissue in a high enough concentration to be effective.

Increased Lipophilicity

Lipophilicity is also an important property for drug molecules because travel through lipophilic membranes in the body is essential for absorption and distribution. For example, the addition of a lipophilic moiety to a drug can help it pass through the blood-brain barrier if the drug needs to reach the brain to be effective.

Selective Targeting To Site

Ideally, a drug would find its way to the appropriate target site without spending much time elsewhere in the body. To help achieve this, prodrugs can be designed to be released in specific organs or tissues where they will be the most efficacious. Different methods may be employed to achieve selective targeting, such as designing a prodrug to target specific transporters or activating enzymes in the body.

Protection From Rapid Elimination

Enzymes in the body can rapidly metabolize some drugs, causing them to be eliminated before an adequate therapeutic effect has taken place. For example, metabolism via enzymes in the digestive system can lead to accelerated drug clearance. A more prolonged duration of action can be achieved through prodrugs that prevent

rapid metabolism, thus extending the half-life of a parent compound. Drugs with adequate exposure times also may require less frequent dosing.

Modern Prodrug Products

Approved by the FDA for patients 6 to 12 years in 2007 and for grown-ups in 2008, Vyvanse was planned as a prodrug of d-amphetamine for the treatment of consideration shortage Hyperactivity Disorder (ADHD). However advertised items at that point, like Adderall® and, not set in stone to be protected and compelling in treating the manifestations of ADHD, there was an acknowledgment inside the clinical local area that those medications introduced difficulties for specific patients just as society (e.g., energizer misuse). In clinical investigations, the prodrug develop of Vyvanse was displayed to empower long haul adequacy for the duration of the day in the two youngsters and grown-ups with once-day by day dosing, tending to a key ADHD neglected need[18]. Adding to Vyvanse's worth, and exhibiting the general worth capability of prodrugs, the main amphetamine-based ADHD drug at the hour of Vyvanse's FDA endorsement, Adderall XR®, was approaching its patent lapse. As a prodrug, Vyvanse could get expanded patent restrictiveness past a regular medication plan in light of the fact that Vyvanse and all prodrugs are for the most part thought about NCEs.

Today, Vyvanse is the marked portion of the overall industry pioneer in ADHD. Be that as it may, later on, Vyvanse may not be the main ADHD prodrug accessible as medication designers, like KemPharm, and its prodrug item competitors of methylphenidate (KP415 and KP484), try to imitate and develop the achievement of Vyvanse. In evidence of-idea investigations of KP415, the information recommended that its plan could consider the advancement of an item with once-every day dosing with a possibly further developed beginning and a long span of activity credits that might help pediatric and juvenile patients with ADHD. Verification of-idea investigations of KP484 exhibited a lengthy delivery d-methylphenidate profile, with a conceivably longer term of activity when contrasted with a current-showcased ADHD methylphenidate item, that might benefit and be most appropriate to the day by day requests of grown-up ADHD patients that don't normally need a fast beginning.

Clinical Applications of Prodrugs

Use of Prodrugs to Overcome Pharmaceutical Barriers

The detailing of another synthetic element with suspected helpful advantages necessitates that the medication be defined into a conveyance structure that is artificially steady, liberated from taste and smell issues (especially in case it is intended for pediatric use or expected for parenteral organization), and the medication should be somewhat liberated from bothering on administration[19].

Masking Taste or Odor Problems

Chloramphenicol is an incredibly severe substance hindering its utilization in pediatricformulations[20]. Chloramphenicol palmitate, a sparingly solvent ester of chloramphenicol, is for all intents and purposes boring in view of its low fluid dissolvability. Since the cooperation of a medication or prodrug with taste receptors requires the medication to be adequately dissolvable in salivation, by bringing the fluid solvency down to cover a taste issue, one risks making a more major issue, i.e., deficient disintegration of the prodrug in the gastrointestinal lot, bringing about inadequate retention. Scent is one more stylish worry for certain medications. Such mixtures are frequently unpredictable fluids or solids with a huge fume pressure that makes them hard to define. An exemplary illustration of this is the unstable mercaptans utilized as tuberculostearic specialists and for the treatment of infection. Ethyl mercaptan has a limit of 25°C and a solid unpalatable scent.

Reduction of Pain Or Irritation At Injection Sites

Pain or aggravation at an infusion site might be brought about by precipitation of the medication, by cell lysis due to one or the other hypo-or hyperosmotic arrangements, the properties of the actual medication, or the destructive activity of the medication at nerve endings[21]. A portion of these issues might identify with the vehicle sythesis or

vehicle pH required for definition purposes. Clindamycin hydrochloride, an anti-microbial with a fluid dissolvability of 3 mg/ml, creates a lot of agony upon intramuscular infusion, while clindamycin 2-phosphate, a prodrug of clindamycin with a solvency of > 150 mg/ml, doesn't cause disturbance or torment upon intramuscular organization. The prodrug has no characteristic antibacterial movement and is changed over to clindamycin in vivo with a half-existence of around 10 minutes by the activity of phosphatase catalysts. Albeit the phosphate ester is identified in the serum for a considerable time span, a large portion of it is eventually cut to clindamycin, with simply 1 to 2% of the portion showing up as an unaltered prodrug in the pee.

Traditional Prodrug Approaches with Phenolic Compounds

Phenolic Compounds (eg. paracetamol)

The conventional methodology has been to 'cover the metabolizable moiety', i.e., to derivatize the phenolic bunch with either an ester or ether type group[22]. These methodologies have met with just peripheral achievement in forestalling foundational leeway of the parent drug. The reason for this horrible showing can be found in crafted by Pang and Gillette (1978) who concentrated on the liver digestion of paracetamol (acetaminophen) and its prodrug, phenacetin (acetophenetidin), in an in vitro perfused liver review. The consistent state hepatic extraction proportion is the small portion of medication wiped out during its section through the liver, and this was estimated for both paracetamol and phenacetin. It was tracked down that the extraction proportion of paracetamol perfused as paracetamol was not exactly the extraction proportion of paracetamol perfused through the liver as phenacetin; i.e., paracetamol delivered from phenacetin by the liver was all the more effectively utilized. This interaction was alluded to by Pang and Gillette as successive digestion. This idea of successive organ digestion might clarify the obvious disappointments seen with most hypothesized ester and ether prodrugs of phenols since the liver and gastrointestinal mucosal cells are rich in esterase and oxidative O-dealkylation (P-450) compounds.

New Prodrug Approaches

Future prodrug research for the anticipation of fundamental digestion of phenols[23]. This includes the plan of initially 'covering' favorable to moieties which are not separated in the gastrointestinal lumen, mucosal cell, or liver, yet by a foundational chemical; consequently, the useful gathering which is the wellspring of the issue is secured. A second methodology that we have been seeking after includes a biochemical procedure. Information on the construction reactivity prerequisites of a specific protein framework (for example phenol transferase) permits one to perceive that the supportive of moiety could be set at another situation in the medication atom, to such an extent that the prodrug is presently not a substrate - due to either steric, electronic or different impacts - for the sulfur pre foundational processing chemical; for example despite the fact that the practical gathering initially assaulted isn't straightforwardly 'concealed', the physicochemical properties of the prodrug are with the end goal that it isn't perceived as a substrate.

Advantages

Prodrugs are intended to beat drug, pharmacokinetic, or pharmacodynamic hindrances like deficient compound steadiness, helpless solvency, inadmissible taste or smell, bothering or torment, lacking oral ingestion, insufficient blood-cerebrum boundary penetrability, checked pre-foundational digestion and harmfulness. Moreover, connection of a favorable to moiety to the dynamic moiety gives an approach to beat the obstructions that hamper the ideal utilization of the dynamic principle[24]

I) Aqueous Solubility

Transscleral retinal conveyance of celecoxib, a calming and hostile to VEGF specialist is limited by its helpless solvency and restricting to the melanin color in choroid-RPE. So for this need the three amide prodrugs of celecoxib were incorporated celecoxib succinimides corrosive (CSA) (Fig. 1), celecoxib maleimide corrosive (CMA) (Fig. 2), and celecoxib acetamide (CAA) (Fig. 3). These showed lesser melanin restricting fondness and limit with a fluid dissolvability of CSA, CMA, and CAA were 300-, 182-and 76-overlap higher, individually than celecoxib. The celecoxib succinimides corrosive was the dissolvable prodrug of celecoxib with diminished melanin restricting which

improves transscleral retinal conveyance of celecoxib [25]. A few different models are Miproxifene phosphate, TAT-59 (anticancer), a phosphate ester of miproxifene/DP-TAT-59, and sulindac (non-steroidal calming), oxide prodrugs of sulindacsulfide, etc[26].

ii) Oral Bioavailability

Gabapentin is an anticonvulsant utilized for the treatment of epilepsy and post-herpetic neuralgia yet experiences imperfect pharmacokinetic properties including saturable assimilation. XP-13512 was created as an oral prodrug. XP-13512 is right now in two-stage IIa clinical preliminaries for post-herpetic neuralgia and fretful leg syndrome[27] .Another such model could be peptidomimeticprodrugs of didanosine (DDI) that show further develop oral bioavailability by means of focusing on gastrointestinal oligopeptide carrier (PepT1) and improving synthetic soundness like 5'- O-L-valyl ester prodrug of DDI exhibited the most elevated layer porousness and restrained take-up of glycylsarcosine (Gly-Sar, a run of the mill substrate of PepT1) by Caco-2 cells[28]

iii) Long-Duration of Action

A model is that the original terminals of buprenorphine esters prodrugs: buprenorphine propionate, enanthate, and decanoate. These created a long-acting antinociceptive result after IM
infusion in rats.[29]

Applications of Prodrugs

The prodrug approach has a broad range of applications as:

Immunomodulators

Leflunomide novel immunomodulatory specialist which displays a solid calming activity. It is a strong helpful specialist in immune system illnesses, unite dismissal, and growth treatment. It is isoxazole subsidiary as a prodrug is totally changed over to its dynamic metabolite A 77 1726 (M1) which hinders the dihydroorotate dehydrogenase, a critical catalyst of the pyrimidine anew synthesis[30]

Antiviral Activity

The principal diastereoselective amalgamation of aryloxy phosphor amide prodrugs of 30-deoxy-20, 30-di hydro thymidine monophosphate (d4TMP) was accounted for were (S)- 4isopropylthiazolidine-2-thione-1 was utilized as a chiral helper to present the stereochemistry at the phosphorus molecule. In the last advance of the created response arrangement, the nucleoside simple d4T was acquainted with a stereochemically unadulterated phosphorodiamidate which prompted the development of the diastereomerically unadulterated phosphor amide prodrugs 8a-d (g95% de)[31]. A purine nucleoside, 2',3'- dihydro-2',3'- dideoxy guanosine (D4G) was observed to be dormant in cell culture and absence of movement of D4G is essentially because of arrangement unsteadiness.

Transdermal Delivery

An examination report states skin pervasion of three novel common prodrugs (MP) in which n-acetyl-glucosamine is combined with a NSAID, either ketoprofen or ibuprofen. They were assessed for transdermal pervasion. MP2 pervades shed snakeskin multiple occasions more prominent than either ibuprofen derivative[32].

Ocular Delivery

Quinidine was seen to be P-GP substrates cum inhibitors[33]. Quinidine, display a questionable blend of three unmistakable connections with P-GP. It was formed to valine as an ester to give Val-quinidine which is a decent substrate for the amino corrosive and peptide carriers present on the cornea. This recognizes different amino corrosive and peptide carriers on the cornea including a Na+-autonomous huge impartial amino corrosive carrier LAT1, a nonpartisan, cationic amino corrosive carrier, and oligopeptide transport framework PepT1. Thus, dipeptide-aciclovir form, Val-Val-ACV, was combined which was severed explicitly by the dipeptidases, aminopeptidases, and cholinesterases and demonstrated to be exceptionally porous across the cornea (2.3-overlap that of aciclovir).

Cholesterol-Lowering Prodrug

Simvastatin (SV) is a lactone prodrug that goes through reversible digestion. In the hydroxy corrosive structure (SVA) it is a powerful inhibitor of HMG-CoA reductase[34]

Thrombolytic Agent

Plasminogen activators incorporate streptokinase, urokinase, and tissue-explicit plasminogen activator tPA conveys the danger of drain as a significant side effect[35]. A heparin/protamine-based prodrug framework was produced for the controlled conveyance of compounds, for example, tissue-type plasminogen activator (tPA). This methodology named as immune response focused on, set off, electrically adjusted prodrug-type technique (ATTEMPTS), would allow counter acting agent coordinated organization of idle tPA, and permit a resulting set off arrival of the dynamic tPA at the objective site[36].

CONCLUSION

In the future for making the treatment more compelling, prodrug advancement seems, by all accounts, to be integral. With the disclosure of catalysts, microorganisms, and receptors in the body, more targets would be investigated that will produce the new time of target-explicit medications with wanted pharmacological, drug profiles and this will assist with accomplishing the best clinical medication application. The use of this prodrug technique will prompt the advancement of more strong essential medications with insignificant side/poisonous impacts. These days, for some sorts of ongoing problems, drugs are essential. Here, the medications which we controlled for such ongoing issues the medications will get gone through the main blood-cerebrum obstruction (BBB) and it will create a reaction. Tragically, certain medications can't capable cross the (BBB)for with the end goal that it should have to get adjusted to cross the obstruction. From this, we come to realize that, later on, we might get progressed information viably.

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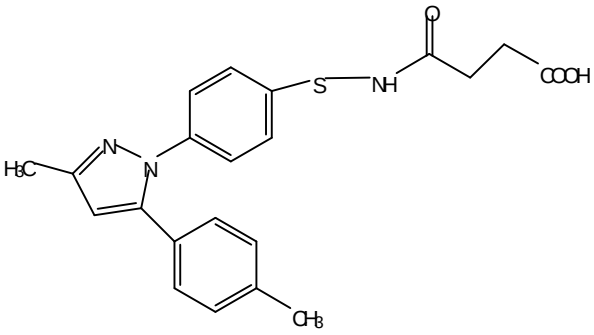

Figure 1: celecoxib Succinamide acid (CSA)

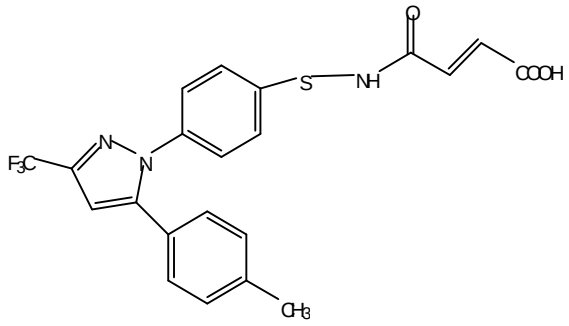

Figure 2: celecoxib Maleimidemide (CMA)

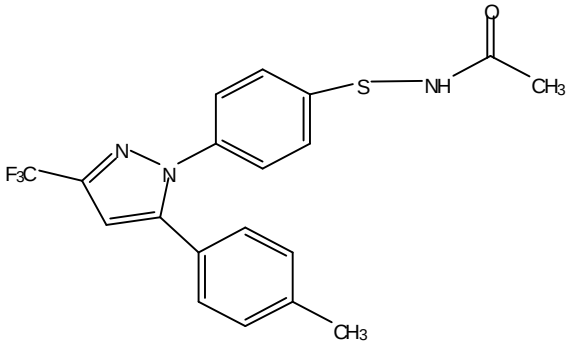

Figure 3 : Celecoxib Acetamide (CAA)

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RESEARCH ARTICLE

IoT-Based Approach for an Automated Irrigation Management System

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ABSTRACT

Agriculture is an important source of income for Indians, and it has had a significant impact on the Indian economy. Crop development for increased yield and higher quality delivery is critical. As a result, optimal conditions and adequate moisture in crop beds can have a significant impact on productivity. Irrigation is mostly done using traditional methods such as stream flows from one end to the other. As a result of this supply, the moisture levels in the fields may vary. The management of the water system can be improved by implementing a planned watering system. This study offers a terrain-specific programmed water system that will decrease manual labor while also optimizing water usage and enhancing agricultural output. . The Arduino kit is combined with a moisture sensor and a Wi-Fi module to create the configuration. Our experimental setup is linked to a cloud framework, and data is collected. After then, cloud services analyze the data and provide suitable recommendations.

Keywords: - Agriculture, Irrigation, Wi-Fi

INTRODUCTION

India is a horticultural nation with a population of over 1.2 billion people, with horticulture employing over 70% of the population. Agriculture is an important source of income for Indians, and it has had a significant impact on the Indian economy. Agriculturists have a wide range of options from which to choose acceptable soil crop goods. Regardless, developing these crops for optimal production and quality delivery is extremely specialized. It can be improved with the assistance of clever bolsters. The management of the water system can be improved by implementing a planned watering system. This study offers a terrain-specific programmed water system that will decrease manual labour while also optimising water usage and enhancing agricultural output. Computerization is

now one of the most important aspects of human life, as it provides comfort, reduces hardship, and allows us to save time.We want to create a framework that allows farmers to automatically deliver water to plants based on their needs and the current moisture level in the soil. Moisture sensors and Arduino chips are used to create a clever water system. We bury a moisture sensor in the soil in the system, which will alert the system to the amount of water present in the soil. The system will verify the amount of water required by a plant using a programme written in C language and specified variables in the programme. Unless a threshold value is achieved, the programme automates the flow of water from a submersible pump if the moisture level is less than the amount of water needed by the plant. This guarantees that the crop receives the proper amount of water without requiring any manual labour or wasting any water. It increases water efficiency, lowers irrigation water costs, and allows for smart irrigation.

Embedded Systems

Embedded systems are PCs that are a part of larger systems and fulfil some of the requirements of such systems. Auto portable control systems, mechanical forms control systems, cell phones, and, on the other hand, small sensor controllers are examples of such systems. Embedded systems encompass a wide range of PC systems, from tiny PC-based gadgets to large systems that check and regulate complicated procedures. The overwhelming quantity of PC systems has a place with embedded systems: embedded systems now account for 99 percent of all registering units.

Arduino

Arduino is an electronic platform based on hardware that is simple to use. It is a free and open source programmed [1]. The Arduino UNO is a low-cost Arduino board that is widely available. The Arduino is a microcontroller-based embedded system. The Arduino's pins are used to read and write values to the system. Microcontrollers come in a variety of shapes and sizes. Some of them, such as the Parallax Basic Stamp, Netmedia's BX-24, Phidgets, and MIT's Handyboard, offer similar functions, however Arduino has the following advantages.

Having an advantage over them

- Low-cost Cross-Platform (Linux, Mac OS, Windows)
- Environment for programming that is simple and straightforward
- Open Source and Extensible software and hardware.

Literature Review

On the topic of irrigation system automation, there has been a lot of study going onto arrives at alternative findings; various other technologies (other microprocessors, different algorithms) were applied. Various scientists have worked with water system frameworks or programmed water sprinkling. They chose several metrics to determine the soil condition and water supply. They also looked into different sources of energy for the sensors. Furthermore, the researchers discussed the development of a sensor system and the design of a control framework in great detail. According to an article on the mechanized water delivery framework for metropolitan local areas, such a framework can be used to effectively manage water assets.[2]The goal of this system is to modernize farming innovation by constructing the appropriate framework pieces utilizing programming segments. The framework is continuous in nature and focuses on the proper condition of the paddy field. One central control centre is used to control another control centre. The RF module's main function is to send messages to the central point and operate the system.[3]

System Development

Soil moisture sensor: The Soil Moisture Sensor (SMS) is a sensor that detects soil dampness content in the dynamic root zone before each scheduled water system occasion and sidesteps the cycle if dampness exceeds a client-defined set point.

Arduino: Arduino is an open source electronics platform that is based on hardware that is simple to use. It comes with its own IDE (Arduino IDE) and open source hardware that can be expanded.

Sensors: The Soil Moisture Sensor (SMS) is a sensor that detects the moisture content of the soil and is connected to the irrigation system controller. The soil moisture sensor measures the moisture content of the soil and prints the

results on the console for viewing. Depending on the plant being watered and the region in which it is irrigated, a threshold value is determined at the start. Within a set delay time, the soil moisture sensors read the data once. When the moisture level rises above the user-defined threshold, the sensor stops reading the data and the control is passed to the Arduino, which activates the pump and begins the system's watering.

Data Acquisitions: Data acquisition is the processing of various electrical or electronic inputs from devices such as sensors, clocks, transfers, and strong state circuits in order to test, break down, or potentially control frameworks and procedures. PC sheets, instruments or frameworks, data loggers or recorders, outline recorders, input modules, yield modules, and I/O modules are all examples of data security instrument types. The data for this study was collected using soil moisture sensors. The principle of dielectric permittivity is used in soil moisture sensors. The quantity of electricity that may pass through the soil is measured by its dielectric permittivity. The dielectric permittivity is determined by the amount of water in the soil. As a result, we could determine the moisture content of the soil by measuring the dielectric permittivity. A fixed (user-defined) threshold value is established, and data is collected until the threshold value is reached. The soil moisture sensor bypasses the reading of the value for one cycle once it has reached the present value.

Threshold value determination: The soil moisture sensor is buried in the soil and water is applied to it. A minimum of one inch of standing water is applied to the soil. The soil, together with the soil moisture sensor, is left in the sun for 24 hours, and if it rains during that time, the process must be again. The soil moisture value is read after twenty-four hours and set as a threshold value. To give the water a little more time to seep in, reduce the moisture level by 20%.

Work Flow Chart

An IoT-based irrigation system works in tandem with sensors on an Arduino kit. Figure 1 depicts the entire system's operation. First, a moisture sensor threshold value is set based on the crop's needs. The humidity readings from the sensor are then compared to the threshold values. Irrigation is continued even if the humidity value falls below.
When the threshold value is achieved, the Arduino kit sends signals to the pump, which turns it off automatically. To expand the connections and link the water pump to the microprocessor, the Arduino microprocessor board is connected to a bread board. To get readings of moisture in farm soil, soil moisture sensors are attached to an Arduino kit. Then, as illustrated in Figure 2, these gathered values are compared to moisture level threshold readings, and the pump is turned on or off accordingly.

Analysis of Data

Data analysis is a method for gathering and composing information in order to obtain useful data.

Data Collection: Soil Moisture Sensors work on the dielectric permittivity concept. The quantity of electricity that may pass through the soil is measured by its dielectric permittivity. The amount of water in the soil is directly proportional to the dielectric permittivity. As a result, we could determine the moisture content of the soil by measuring the dielectric permittivity. Soil Moisture Sensors are buried, with the Arduino chipset on the other end. After a predetermined amount of time, the soil moisture sensor analyses the dielectric permittivity of the soil. These values are delivered to the Arduino chipset and displayed on the system accordingly.

Data Analysis: At the start of the method, a threshold value is set. The following are the measures to take before setting the threshold value: The water flow is opened after the soil moisture sensor is buried in the soil. A minimum of one inch of water should be allowed to sit on the soil. For twenty-four hours, the soil is exposed to the sun. In the event that it rains during this time, the procedure must be restarted from the beginning. After twenty-four hours, the moisture value is recorded, and the threshold value is set at a 20% divergence from the moisture value. Following the acquisition of the threshold value, the soil moisture sensors are permitted to read the moisture content at predetermined intervals. The information is gathered and compared to a set of criteria. Following the comparison, the system has two options:

If the moisture content exceeds the threshold value, this is the first case. When the moisture content of the soil is measured using the soil moisture sensor and found to be higher than the threshold value, the value is read again after a certain period of time and compared. This technique is repeated until Case 2 appears. If the moisture content is less than the threshold value, Case 2 applies.

When the moisture content of the soil, as measured by the soil moisture sensor, is less than the threshold value, the system skips one round of reading the readings. To notify the pump of a condition change, a signal is transmitted. . (From LOW to HIGH) The valve for the strip whose moisture content is less than the threshold value is opened, allowing water from the pump to flow.

CONCLUSION

The majority of India's land is used for agriculture. Agricultural outputs require irrigation. The crop production is better and more optimally irrigated fields. As a result of this effort, a smart irrigation system based on IoT with a humidity sensor has been developed. It can monitor the moisture content of the soil in the farm and generate moisture data using sensors. . As a result, irrigation-based decisions are made automatically by the system to start the water pump and divert the flow of the pump motor for irrigation. A well-designed system may irrigate a field with less water. For improved yields, the crop can be kept at its appropriate moisture threshold levels.

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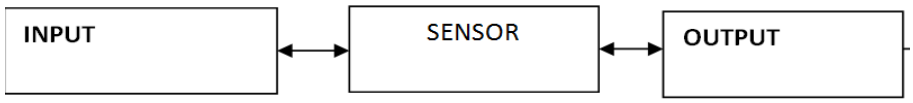

Fig 1: Block diagram

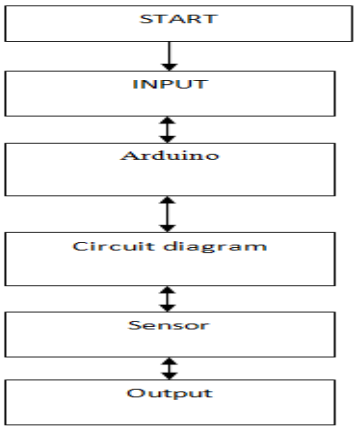

Fig 2: System Implementation

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RESEARCH ARTICLE

Antibiogram of *Pseudomonas aeruginosa* Isolates from Clinical and Environmental Sources

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ABSTRACT

The present study was undertaken to determine the Antibiogram of *Pseudomonas aeruginosa* isolate from clinical and environmental sources. *Pseudomonas aeruginosa* is an important pathogen which causes nosocomial infections in immuno compromised patients, in recent times; it has emerged as a widespread Multi Drug Resistant (MDR) pathogen which requires antibiotic susceptibility testing on a regular as well as a periodic basis. A prospective study was undertaken with 64 samples (surgical sites infection, diabetic foot ulcer, puss and wound swabs) which were gotten from laboratories of Abubakar Tafawa Belewa University teaching hospital Bauchi, Bauchi state and with 128 samples which were obtained from random sites at the Abubakar Tafawa University campus Yelwa, Bauchi state. Standard microbiological techniques and Kirby-Bauer disc diffusion antibiotic susceptibility testing was carried out for the analyses of the resistance or susceptibility of the microorganism from the different sources.64 and 128 samples were collected from clinic and environmental sources, respectively, *P. aeruginosa* were isolated from inpatients and environmental samples, with Total resistance 85 and percentage Resistance 66.4%,whileTotal susceptive 43percentage susceptive 33.6%.Also for clinic specimen**.** Total resistance 49 percentage Resistance 76.5% while total susceptibility 15 and percentage susceptibility 23.4%,Strategies of optimal prescribing, including control of antibiotic usage, *P. aeruginosa* infections in patients, appear to be leading priorities which help in improving therapeutic gains in such patients. This study examined the prevalence of *P. aeruginosa* and its susceptibility patterns to different antibiotics.

Keywords: Antibiogram, Infection, Multi Drug Resistant, *Pseudomonas aeruginosa*.

INTRODUCTION

Pseudomonas aeruginosa is a common Gram-negative, rod-shaped bacterium that can cause disease in plants and animals, including humans. A species of considerable medical importance, *P. aeruginosa* is a multidrug resistant pathogen recognized for its ubiquity, it's intrinsically advanced antibiotic resistance mechanisms, and its association with serious illnesses – hospital-acquired infections such as ventilator-associated pneumonia and various sepsis syndromes (Ahmad *et al*., 2016). Biosurfactants are divided into low molecular weight compounds such as glycolipids or lipopeptide and high molecular weight compounds such as polysaccharides, proteins, lipopolysaccharides or lipoproteins (Ramrajan *et al*., 2017). The organism is considered opportunistic insofar as serious infection often occurs during existing diseases or conditions – most notably cystic fibrosis and traumatic burns. It is also found generally in the immunocompromised but can infect the immunocompetent as in hot tub folliculitis. Treatment of *P. aeruginosa* infections can be difficult due to its natural resistance to antibiotics. When more advanced antibiotic drug regimens are needed adverse effects may result.

It is citrate, catalase, and oxidase positive. It is found in soil, water, skin flora, and most man-made environments throughout the world. It thrives not only in normal atmospheres, but also in low-oxygen atmospheres, thus has colonized many natural and artificial environments. It uses a wide range of organic material for food; in animals, its versatility enables the organism to infect damaged tissues or those with reduced immunity. The symptoms of such infections are generalized inflammation and sepsis. If such colonization's occur in critical body organs, such as the lungs, the urinary tract, and kidneys, the results can be fatal. Because it thrives on moist surfaces, this bacterium is also found on and in medical equipment, including catheters, causing cross-infections in hospitals and clinics. It is also able to decompose hydrocarbons and has been used to break down tarballs and oil from oil spills (Das *et al*., 2016; Davane *et al*., 2014). *P. aeruginosa* is not extremely virulent in comparison with other major pathogenic bacteria species – for example *Staphylococcus aureus* and *Streptococcus pyogenes* though P. *aeruginosa* is capable of extensive colonization, and can aggregate into enduring biofilms.

MATERIALS AND METHOD

Study area

The study was carried out in Abubakar Tafawa Balewa University Teaching Hospital (ATBUTH). It is located at North East zone of Nigeria and it is situated within guinea savannah region. Raining season April and ends in October with a mean annual rainfall of 750-10151 of 4,676,465, is densely populated with area of about 54,837km square. Most inhabitant of this locality are mostly farmers covering about 40%, civil servant covering 40-45% and commercial motorcycle/tricycle drivers thereby increasing the risk of having accident.

Collection of samples

Clinical specimen

A total number of 25 wound swab or aspirated pus in syringe from surgical and burn wards is collected before wound dressing. All samples are collected from patient after obtaining a written informed consent from the patient and processed following the standard laboratory techniques. Approval of this study was obtained from Bauchi State Ministry of Health ethical review board on July 25th 2018. Environmental samples were collected from random location in Abubakar Tafawa Balewa University Yelwa campus Bauchi.

Sampling processing

The wound swab was inoculated on Nutrient Agar and the plates are incubated at 37oc for 48hours aerobically. All isolates are tested for antimicrobial susceptibility to determine the resistance pattern of each isolates using Kirby-Bauer disc diffusion techniques on Muller Hinton Agar.

Environmental samples

Soil samples were collected from random sites at Abubakar Tafawa Belewa University, Bauchi. Samples were collected 5 cm below the land surface in sterile containers. One gram of each soil sample was dispersed in sterile test tubes. Thereafter, a series of dilution from 10-2 to 10-10 were prepared in 9 ml of distilled water. Afterwards 0.1 ml was dispensed in the growth media and was incubated for 48hrs.

Antibacterial assay

Susceptibility to antibiotics of the bacteria isolates were assayed according to the Kirby – Bauer disc diffusion method on Mueller-Hinton agar (Oxoid) (Bauer *et al*., 1996). All the plates were incubated for 20 minutes before inoculation to allow excess moisture to dry. After antibiotic sensitivity disc (Maxidisc) containing Gentamycin 10ug, Augmentin 30ug, Pefloxacine 10ug, Chloramphenicol 30ug, Ciprofloxacin 10ug, Cotrimazole 30ug, Amoxicillin 30ug, Sparfloxacin 10ug, Ofloxacine 10ug, and Streptomycin 30ug for gram negative bacteria and Gentamycin 10ug, Pefloxacine 30ug, Ciprofloxacin 10ug, Ampiclox 30ug, Ofloxacine 30ug, Amoxicillin 30ug, Cefuroxime 20ug, Streptomycin 30ug, Ceftriazone 25ug, and Erythromycin 10ug for gram positive bacteria were placed on the cultured media before closing the plate as described by Bolaji *et al*., (2011). After 30 minutes, the plates were incubated for 24 hours. After incubation, a ruler was used to measure the diameter of each zone of inhibition in mm on the underside of the plate as described by Igbinosa *et al*., (2017). The interpretation as 'Sensitive' or 'Resistant' was done on the basis of diameters of zones of inhibition of bacterial growth as recommended by Clinical and Laboratory Standards Institute (CLSI, 2012).

RESULT AND DISCUSSION

The chapter contains the result obtained on baseline characteristic, the Antibiograme of *Pseudomonas aeruginosa* isolated from clinical and environment source. The above table shows that *P.aeruginosa* strains were much more resistant to samples from the environment, at which ceftriaxone, impenem and oflaxin were at the top of the chat for effective resistance. Also for clinical samples tetraclcin, ceftioxine and septrim were very much resisted on the other hand ciprofaxine, levofloxacin, amoxicillin; pefloxacin and tetracycline were effective in action on both samples from clinic and environmental sources. However it was observed that *P.aeruginosa* that was found in the environment resisted 70% of the antibiotics (Figure 1).

Pseudomonas aeruginosa is a leading cause of hospital acquired infections with a high propensity to develop, acquire or transfer antimicrobial resistance genes (Gales *et al.,* 2001). This phenomenon is associated with increased rates of morbidity, mortality and high cost of treatment. In this study, am reporting on the prevalence and antimicrobial susceptibility pattern of this organism**.** The organism was isolated from all 192 specimen types (Wound Infection, Diabetic Foot Ulcer, Surgical Site Incision and Environmental), antimicrobial resistance patterns revealed a total of ten patterns of which the most prevalent displayed resistance to cefotaxime, gentamicin and tetracycline (CLX GEN AUG) and they accounted for MAR 0.33 (33.3%) of *P. aeruginosa* isolate. This was closely followed by the pattern showing resistance to cefotaxime, gentamicin, and tetracycline (CLX GEN TCN) MAR 0.33 (33.3%). The least resistance patterns were noted for cefotaxime and gentamicin (CTX GEN) MAR 0.22 (22.2%), gentamicin and tetracycline (GEN TCN) and ciprofloxacin, and tobramycin (CHR TCN) exhibited by MAR 0.22 (22.2%) of the isolates respectively. Approximately 98% of isolates were resistant to three or more antibiotics. Of these, 91.8% were resistant to two or more drugs, the majority coming from environmental samples. Multi drug resistance in environmental isolates might be linked to the uncontrolled disposing of antibiotics and chemicals into the environment creating a selective pressure on these drugs. The use of antibiotics in hospital and the community at large serves as a major selective pressure for antibiotic resistant bacteria (Moreira *et al*., 2002). Multi drug resistant nosocomial infections by this organism are increasing worldwide. The existence of metallo β lactamases and extended spectrum β lactamase producing strains exhibiting resistance to most β lactams antimicrobial agents greatly complicate the clinical management of patients infected with such multi drug resistant strains. *Pseudomonas aeruginosa* resistance to

antibiotics is a serious problem in hospitals in Africa. A number of similar studies conducted in South Africa, Cote d'Ivoire, Nigeria and Tunisia (Kamoun *et al*., 1992; Rotimi *et al*. 1994) documented the existence of multi resistant strains of *P. aeruginosa* responsible for nosocomial infections.

CONCLUSION

This high level resistance is thought to be plasmid mediated. Strategies of optimal prescribing, including control of antibiotic usage, coupled with periodic studies on MDR *P. aeruginosa* infections in patients, appear to be leading priorities which help in improving therapeutic gains in such patients. Also the use of chemicals on land should be reduced because it tends to create space for more room in the ability for *p. aeruginosa* to improve on its ability to resist drug effect. This study examined the prevalence of *P. aeruginosa* , and its susceptibility patterns to different antibiotics.

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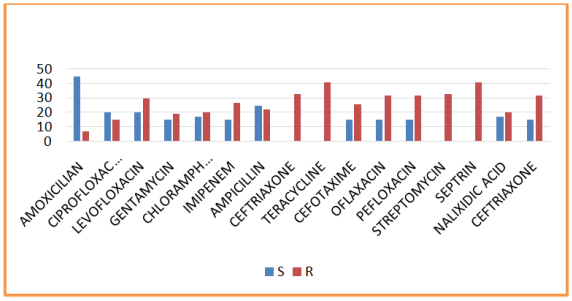

Figure 1. Frequency of occurrence of *P. aeruginosa* in clinical and environmental source. DFU= Diabetic foot ulcer, SSI= surgical site infection, WI = wound infection

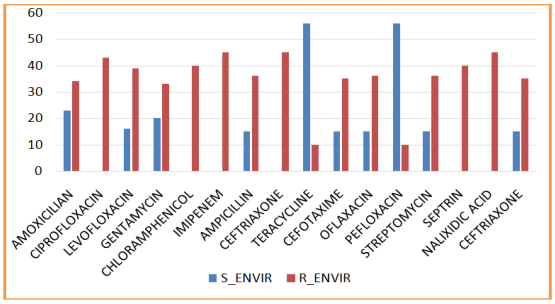

Figure 2. Antimicrobial susceptibility pattern for environmental sample(According to CLSI 2014).

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REVIEW ARTICLE

A Review On: International Council of Harmonisation (ICH) Guideliness

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ABSTRACT

At the principal ICH Steering Committee (SC) meeting of ICH the Terms of Reference were concurred and it was concluded that the Topics chose for harmonization would be separated into Safety, Quality and Efficacy. The introduction of ICH occurred at a gathering in April 1990, facilitated by EFPIA in Brussels. The International Council for Harmonization (ICH), in the past the International Conference on Harmonization (ICH) held the debut Assembly gatherings on 23 October 2015 setting up ICH as a global affiliation. For most nations, regardless of whether they had started item enlistment controls before, the 1960s and 1970s saw a fast expansion parents in law, guidelines and rules for revealing and assessing the information on wellbeing, quality and adequacy of new restorative items.

Keywords: International council of harmonisation (ICH), Steering committee, Quality guidelines, Safety guidelines, Efficacy guidelines. Multidisciplinary guidelines.

INTRODUCTION

At the principal ICH committee (SC) meeting of ICH the Terms of Reference were concurred and it had been concluded that the Topics chose for harmonization would be separated into wellbeing, Quality and Efficacy to reflect the three guidelines which are the justification behind embracing and supporting new remedial things. The introduction of ICH occurred at a gathering in April 1990, facilitated by EFPIA in Brussels. Agents of the administrative offices and industry relationship of Europe, Japan and the US met, principally, to design an International Conference and terms of reference of ICH. First decade saw tremendous improvement in the progression of Tripartite ICH Guidelines on Safety, Quality and Efficacy focuses. Work was likewise attempted on

various significant multidisciplinary themes, which included MedDRA (Medical Dictionary for Regulatory Activities) and the CTD (Common Technical Document). The mission of ICH is to make proposals towards accomplishing more prominent harmonization in the understanding and utilization of specialized rules and necessities for drug item enrollment and the upkeep of such enlistments. It likewise screens and update orchestrated specialized prerequisites prompting a more noteworthy shared acknowledgment of innovative work information. ICH assists with working with the reception of new or worked on specialized innovative work approaches which update or replace current practices. It assists with creating strategy for the ICH Medical Dictionary for Regulatory Activities Terminology (MedDRA) while guaranteeing the logical and specialized support, advancement and scattering of MedDRA as a normalized word reference which works with the sharing of administrative data globally for restorative items utilized by people.

HISTORY [9,10]

The International Council for Harmonization (ICH), some time ago the International Conference on Harmonization (ICH) held the debut Assembly gatherings on 23 October 2015 building up ICH as a worldwide affiliation, a legitimate element under Swiss law.This step based upon a 25-year history of fruitful conveyance of orchestrated rules for worldwide drug improvement just as their guideline, and a more drawn out standing acknowledgment of the need to fit.

The Need to Harmonise [11-15]

The acknowledgment that it was critical to have a free assessment of therapeutic items before they are permitted available was reached at various occasions in various districts. Anyway as a rule the acknowledgment was driven by misfortunes, like that with thalidomide in Europe during the 1960s. For most nations, regardless of whether they had started item enlistment controls before, the 1960s and 1970s saw a quick expansion parents in law, guidelines and rules for announcing and assessing the information on wellbeing, quality and viability of new restorative items. The business, at that point, was turning out to be more worldwide and looking for new worldwide business sectors; but the difference in specialized prerequisites from one country to another was to such an extent that industry thought that it is important to copy many tedious and costly test methods, to showcase new items, globally. The pressing need to justify and fit guideline was incited by worries over increasing expenses of medical care, heightening of the expense of R&D and the need to meet the public assumption that there ought to be at least deferral in making protected and effectual new therapies accessible to patients out of luck.

Initiation of ICH [16-20]

Harmonization of administrative prerequisites was spearheaded by the EC, Europe, during the 1980s, as the EC, Europe moved towards the improvement of a solitary market for drugs. The achievement accomplished in Europe showed that harmonization was possible. Simultaneously there were conversations between Europe, Japan and the US on opportunities for harmonization. It was, notwithstanding, at the WHO Conference of Drug Regulatory Authorities (ICDRA), in Paris, in 1989, that specific plans for action began to show up. Before long a while later, the specialists moved toward International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) to talk about a joint administrative industry drive on global harmonization, and ICH was imagined. At the key ICH Steering Committee meeting of ICH the Terms of Reference were agreed and it was expected that the Topics decided for harmonization would be separated into Safety, Quality and Efficacy to reflect the three principles which are the justification behind supporting and endorsing new restorative things.

THE EVOLUTION OF ICH [21-26]

Since ICH's initiation in 1990, the ICH connection has gradually progressed. ICH's first decade saw colossal improvement in the progression of ICH Guidelines on Safety, Quality and Efficacy focuses. Work was additionally embraced on various significant multidisciplinary subjects, which included MedDRA (Medical Dictionary for Regulatory Activities) and the CTD (Common Technical Document). As ICH began another thousand years, the need to grow correspondence and spread of data on ICH Guidelines with non-ICH areas turned into a key concentration.

Consideration was additionally coordinated all through the second decade towards working with the execution of ICH Guidelines in ICH's own locales and keeping up with previously existing ICH Guidelines as science and innovation kept on advancing. Presently in its fourth decade of movement, ICH's consideration is coordinated towards broadening the advantages of harmonization past the establishing ICH locales. A critical advance was taken in 2015 to work with this which saw ICH going through a progression of hierarchical changes. These progressions comprised various changes including: expanding worldwide effort; changing ICH's administration structure; dispersing more data on ICH cycles to a more extensive number of partners; and building up ICH as a legitimate element to accommodate a more steady working construction.

The subsequent ICH affiliation sets up an Assembly as the overall overseeing body determined to concentrate worldwide drug administrative harmonization work in one scene that permits drug administrative specialists and outstandingly concerned industry associations to be all the more effectively engaged with ICH's harmonization work.

STRUCTURE OF ICH [27-28]

1. ICH Assembly
2. ICH Management Committee
3.MedDRA Management Committee
4.ICH Secretariat

THE ICH ASSEMBLY [29,30]

It works in uniting all Members and Observers of the ICH Association as the all-encompassing overseeing assortment of ICH. It takes choices on particular matters, for example, on the reception of ICH Guidelines, affirmation of new Members and Observers, and the ICH Association's work plans and financial plan. Part experts doled out by the Assembly are kept up with by ICH Coordinators who address every Member to the ICH Secretariat dependably.

THE ICH MANAGEMENT COMMITTEE (MC) [31]

The body which oversees the functional parts of ICH in the interest of all Members, counting regulatory and monetary issue and oversight of the Working Groups (WGs).

THE MEDDRA MANAGEMENT COMMITTEE (MC) [32,33]

It has liability regarding giving guidance of MedDRA, ICH's normalized clinical phrasing. The MedDRA MC is liable for overseeing, supporting, and working with the upkeep, improvement, and scattering of MedDRA.

THE ICH SECRETARIAT [34-36]

It is answerable for everyday administration of ICH, planning ICH exercises just as offering help to the Assembly, the MC and Working Groups. The ICH Secretariat additionally offers help to the MedDRA MC. The ICH Secretariat is situated in Geneva, Switzerland. The advancement of another fit rule and its execution (the formal ICH technique) includes 5 stages

FORMAL ICH PROCEDURE [37-39]

Step1 : Consensus building
Step2 : Confirmation of six party consensus
Step3 : Regulatory Consultation and Discussion
Step4 : Adoption of an ICH Harmonized Tripartite guideline
Step5:Implementation

PROCESS OF ICH HARMONISATION FORMAL ICH PROCEDURE [40,41]

The methodology is started with the underwriting by the SC of a Concept Paper and Business Plan. An Expert Working Group (EWG) with participation as indicated by the Concept Paper is therefore settled. The EWG attempts to foster a draft Guideline and bring it through the different strides of the methodology which come full circle in Step 5 and the execution in the ICH locales of a Harmonized Tripartite Guideline.

STEP 1: CONSENSUS BUILDING [42,43]

The EWG attempts to set up an agreement draft of the specialized report, in light of the targets set out in the Concept Paper. Work is led by means of email, video chats and web gatherings. Whenever supported by the SC, the EWG will likewise meet vis-à-vis at the half-yearly SC gatherings. Interval investigates the advancement of the draft are made to the SC consistently. At the point when agreement on the draft is reached among each of the six party EWG individuals, the EWG will sign the Step 1 Experts close down sheet. The Step 1 Experts Technical Document with EWG marks is then submitted to the Steering Committee to demand reception under Step 2 of the ICH interaction.

STEP 2A: CONFIRMATION OF SIX-PARTY AGREEMENT ON THE TECHNICAL DOCUMENT [44,45]

Step 2a is arrived at when the SC concurs, in light of the report of the EWG, that there is adequate logical agreement on the specialized issues for the Technical Document to continue to the following phase of administrative meeting. This arrangement is affirmed by something like one of the SC individuals for every one of the six ICH parties marking their consent. Step 2b: Adoption of draft Guideline by Regulatory Parties based on the Technical Document, the three ICH administrative gatherings will make the moves they consider significant to foster the draft Guideline.

STEP 3: REGULATORY CONSULTATION AND DISCUSSION [46]

Stage 3 happens in three unmistakable stages: administrative interview, conversation and conclusion of the Step 3 Expert Draft Guideline.

ICH HARMONIZATION PROCESS [47]

1. Selection of New Topic for Harmonization
2. Consensus on draft Technical document
3. Endorsement by the Assembly
4. Assembly adoption of ICH Guidelines
5. Regulatory Consultation and Discussion
6. Implementation

MISSION [48-50]

1. ICH decreased the duplication of testing did during the innovative work of new human medications. ICH's central goal is to accomplish more noteworthy harmonization in the translation and utilization of specialized rules and its necessities for drug item enrollment.

2. ICH is an exceptional endeavor that unites the medication administrative specialists and the drug business of Europe, Japan and the United States.

3. Regulatory harmonization offers many direct advantages to both administrative specialists and the drug business with gainful effect for the assurance of general wellbeing. Key advantages include: forestalling duplication of clinical preliminaries in people and limiting the utilization of creature testing without compromising security and adequacy.

ORGANIZATION [51]

Since its declaration of hierarchical changes in October 2015, ICH has developed as an association and presently incorporates 18 Members and 33 Observers.

STEERING COMMITTEE [52-56]

The ICH Steering Committee (SC) is the administering body that directs the harmonization exercises. Since its foundation in 1990, every one of its six cosponsors (EU, EFPIA, MHLW, JPMA, FDA, PhRMA) has had two seats on the SC. Different gatherings have a critical interest in ICH and have been welcome to select Observers to the SC. The three Observers are the World Health Organization (WHO), Health Canada and the European Free Trade Association (EFTA). The IFPMA partakes as a nonvoting individual from the SC.

1. WHO (World Health Organization)
2. Health Canada
3. EFTA (European Free Trade Association)
4. IFPMA (International Federation of Pharmaceutical Manufacturers and Associations)
5. PhRMA (Pharmaceutical Research and Manufacturers of America)
6. EU (European Union)
7. EFPIA (European Federation of Pharmaceutical Industries and Associations)
8. MHLW (Ministry of Health, Labor and Welfare)
9. JPMA (Japan Pharmaceutical Manufacturers Association)
10. FDA (US Food and Drug Administration)

GLOBAL COOPERATION GROUP [57-59]

The Global Cooperation Group (GCG) was initially shaped as a subcommittee of the ICH Steering Committee in 1999 in light of a developing interest in ICH Guidelines past the three ICH areas. A couple of years after the fact, perceiving the need to connect effectively with other harmonization drives, delegates from five Regional Harmonization Initiatives (RHIs) were welcome to take part in GCG conversations, specifically, APEC, ASEAN, EAC, GCC, PANDRH and SADC. A further extension of the GCG was concurred in 2007 and controllers were welcomed from nations with a background marked by ICH Guidelineimplementation and additionally where significant creation and clinical exploration are done (Australia, Brazil, China, Chinese Taipei, India, Republic of Korea, Russia and Singapore).

MEDDRA MANAGEMENT [60-62]

Board The MedDRA Management Board, delegated by the ICH Steering Committee, has generally liability regarding bearing of MedDRA, an ICH normalized word reference of clinical phrasing. The Board supervises the exercises of the MedDRA "Upkeep and Support Services Organization" (MSSO), which fills in as the storehouse, maintainer, engineer and wholesaler of MedDRA. The Management Board is made out of the six ICH Parties (EU, EFPIA, MHLW, JPMA, FDA, PhRMA), the Medicines and Healthcare items Regulatory Agency (MHRA) of the UK, the Health Canada and the WHO (as Observer). The IFPMA goes about as a non-casting a ballot onlooker on the Management Board and seats the Board.

SECRETARIAT [63,64]

The ICH Secretariat is situated in Geneva, Switzerland. Its staff part is liable for everyday administration of ICH, to be specific arrangements for, and documentation of, gatherings of the Steering Committee and its Working Groups. The ICH Secretariat likewise offers authoritative help for the ICH Global Cooperation exercises and the ICH MedDRA Management Board.

FACILITATORS[65,66]

Essential to the smooth running of ICH has been the assignment, by every one of the six co-supports, of an ICH Coordinator to go about as the principle contact point with the ICH Secretariat. Facilitators guarantee legitimate conveyance of ICH reports to the fitting people from their party (SC individuals, Topic Leaders, Experts) and are liable for appropriate development on activities by their separate party inside alloted cutoff times.

ICH GUIDELINES [67]

ICH guidelinesare mainly categorised into four types they are

1. Quality guidelines
2. Safety guidelines
3. Efficacy guidelines
4. Multidisciplinary Guidelines

QUALITY GUIDELINES [68-72]

Harmonization achievement in the Quality region incorporate significant achievements, for example, the conveying of soundness considers, deciding applicable edges for debasements testing and a more adaptable way to deal with drug quality dependent on Good Manufacturing Practice (GMP) hazard the executives.

SAFETY GUIDELINES [73-78]

ICH has arranged a far reaching set of wellbeing rules to uncover potential dangers like cancer-causing nature, reprotoxicity and genotoxicity. A new finding has been a non-clinical testing outline for deciding the QT span prolongation obligation.

EFFICACY GUIDELINES [79-85]

The Efficacy rules are worried about the plan, conveying, andsafety andreporting of clinical preliminaries. It likewise gives data identified with novel sorts of meds got from biotechnological strategies and the utilization of pharmacogenomics methods to create better designated drug.

MULTIDISCIPLINARY GUIDELINES [86-89]

These rules contains points which are special, and don't squeeze into one of the Quality, Safety and Efficacy rules class. Multidisciplinary Guidelines portrays about Common Technical Document (CTD), clinical terminology (MedDRA), and the advancement of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

WORKING GROUPS [90-94]

For every one of the specialized points which have been chosen for harmonization in the primary period of exercises, the SC selected a Working Group to survey the distinctions in necessities between the three locales and foster logical agreement needed to accommodate those distinctions. Working gatherings don't have a fixed "enrollment" however every one of the six gatherings have selected a Topic Leader (and, as often as possible, a Deputy Topic Leader) as the contact for the theme. The Observers to ICH, the Pharmacopeia specialists and agents from the self-medicine industry and the conventional business have been welcome to take an interest in different working gatherings. There are a few distinct sorts of ICH working gatherings that can be recognized:

1. EWG: Expert Working Group is accused of fostering an orchestrated rule that meets the goals in the Concept Paper and Business Plan.
2. IWG: Implementation Working Group is entrusted to foster Q&A's to work with execution of existing rules.
3. Informal Working Group: Is shaped before any authority ICH harmonization action with the destinations of creating/concluding a Concept Paper, just as fostering a Business Plan.
4. Discussion Group: Is a gathering set up to examine explicit logical contemplations or perspectives for example Quality Therapy Discussion Group (GTDG), and ICH and Women Discussion Group.

ICH is advantageous for the brand-name pharmaceutical companies [95-98]

To put up drugs for sale to the public as fast and reasonably as could be expected, and in whatever number nations as would be prudent, the drug business needs the ICH to:

1. Agree on one bunch of logical standards for running clinical preliminaries;

2. Reduce the quantity of exploration creatures and human guineas pigs fundamental for testing (hence diminishing costs);
3. Establish one bunch of guidelines for the assembling system of new medications;
4. Ensure comparable application measures for drug endorsement in all nations; Ensure that exploration discoveries from one part nation will be acknowledged by any remaining nations (for certain exemptions for uncommon populaces).

Those actions would assist with offering drugs for sale to the public all the more rapidly. Nobody would differ with getting rid of pointless and uninformative duplication of exploration. Nonetheless, with regards to compromising and shortening courses of events, it's another matter. For a large portion of people in general, speed of endorsement isn't the significant thought. More significant is assurance of general wellbeing, and new drugs that have been totally tried for security and that meet genuine human requirements. On the off chance that the ICH interaction prompts compromises in wellbeing guidelines through a hurry to "blend" to the most minimal of existing principles, there is valid justification to be concerned.

THE FUTURE OF ICH [99-104]

1. ICH has finished a significant stage. Key rules are currently being carried out in the space of Efficacy, Quality and Safety in the three ICH areas. The association has set up an upkeep strategy to guarantee that the rules keep on mirroring the most recent logical turns of events and best practice.
2. These support exercises are fundamental for the fate of ICH, and to guarantee that harmonization proceeds. A few more aspiring rules are a work in progress, like Good Manufacturing Practice (GMP) for Active Pharmaceutical Ingredients (APIs), Pharmacopeias Harmonization.
3. The Common Technical Document and its electronic partner will be accessible in under two years, both set to change methodology for administrative dossier accommodation essentially. The association has perceived the significance of making accessible data on the ICH cycle and rules to non-ICH areas with the foundation of the Global Cooperation Group.
4. As well as making data accessible, the gathering will go about as an asset in the arrangement, and even acknowledgment, of a considerable lot of the rules [19]. Different subjects that may now go to the front are those like the Harmonization of Regulatory Review Procedures.
5. While the rules set a typical norm for improvement, there is no shared trait in audit. By advancing more noteworthy cooperation between the skillful specialists, to such an extent that there is more straightforwardness in the audit cycle, it is a sensible expectation that a typical norm of survey will be accomplished.
6. Such an improvement is something that the business ought to effectively support through the ICH discussion, as the advantages would be huge.

CONCLUSION

Finally, ICH looks to the future. It has established a structure to maintain the guidelines, and at the same time is looking to make available information on the ICH process and guidelines to non-ICH regions with the establishment of the Global Cooperation Group. As well as making information available, the group will act as a resource in the understanding, and even acceptance, of many of the guidelines. From an industry perspective globalization is arguably the most important issue it faces, and the ability of these guidelines to effect intra-company globalization is a facet of ICH that cannot be ignored. This is already happening within companies. Its value has not been quantified; however, the companies able to embrace these principles today will be the world leaders tomorrow. Companies who fail to see the value of harmonization—the value that is already being felt by the scientists carrying out the development, and the value that is yet to be realized in the full drug development cycle— will be left at the starting line of the industry's globalization race.

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Table No: 1- ICH QUALITY GUIDEELINES

S.No.	GUIDELINES
1.	**Q1A-Q1F STABILITY:** Q1A: Stability testing of new medication substances and items Q1B: Stability testing: photostability testing of new medication substances and items Q1C Stability testing for new measurement structures Q1D Bracketing and matrixing plans for solidness testing of new medication substances and items Q1E Evaluation of solidness information Q1F Stability information bundle for enlistment applications in climatic zones III and IV
2.	**Q2 Analytical validation:** Validation of analytical procedures
3.	**Q3A-Q3D Impurities:** Q3A Impurities in new medication substances Q3B Impurities in new medication items Q3C Impurities: Guidelines for leftover solvents Q3D Impurities: Guidelines for natural exemptions
4.	**Q4A-Q4B Pharmacopeias:** Q4A: Pharmacopeial Harmonization Q4B Evaluation and suggestion of pharmacopeial texts for use In the ICH locales
5.	**Q5A-Q5E Quality of biotechnological products:** Q5A Viral security assessment of biotechnology items got from cell lines of human or creature beginning Q5B Analysis of articulation develop in cells utilized for creation of r-DNA determined protein items Q5C Stability testing of biotechnological/natural items Q5D Derivation and portrayal of cell substrates utilized for creation of biotechnological/natural items Q5E likeness of biotechnlogical/natural items subject to changes in their assembling interaction
6.	**Q6A-Q6B Specifications:** Q6A Test methods and acknowledgment standards for new medication substances and new medication items: Chemical substances Q6B Test methods and acknowledgment standards for biotechnological/organic items
7.	Q7 Good manufacturing practices for Active pharmaceutical ingredients
8.	Q8 Pharmaceutical development
9.	Q9 Quality risk management
10.	Q10 Pharmaceutical quality system
11.	Q11 Development and manufacture of drug substances (Chemical entities and biological entities)

Table No : 2-ICH SAFETY GUIDELINES

S.No.	GUIDELINES
1.	**S1A-S1C Carcinogenicity studies:** S1: Rodent cancer-causing nature reads for human Pharmaceuticals S1A: Need for cancer-causing nature investigations of Pharmaceuticals S1B: Testing for cancer-causing nature of Pharmaceuticals
2.	**S2 Genotoxicity studies** S2 (R1) Guidance on genotoxicity testing anddata interpretation for Pharmaceuticals intended for human use
3.	**S3A-S3B Toxicokinetics and pharmacokinetics:** S3A note for direction on toxicokinetics: The evaluation of foundational openness in harmfulness contemplates S3B Pharmacokinetics: Guidance for rehashed portion tissue dispersion considers
4.	**S4 Toxicity testing:** S4 Duration of chronic testing in animals (Rodent and non rodent toxicity testing)
5.	**S5 Reproductive toxicology:** S5 Detection of toxicity to reproduction for medicinal products and toxicity to male fertility
6.	**S6 Biotechnological products:** S6 Preclinical safety Evaluation of biotechnology derived Pharmaceuticals
7.	**S7-S7B Pharmacology studies:** S7A Safety pharmacology reads for human Pharmaceuticals S7B The non clinical assessment of the potential for postponed ventricular repolarization by human Pharmaceuticals
8.	**S8 Immunological Studies:** S8 Immunotoxicity studies for human Pharmaceuticals.
9.	S9 Nonclinical evaluation for anti cancer Pharmaceuticals
10.	S10 Photosafety evaluation of Pharmaceuticals

Table No : 3- ICH EFFICACY GUIDELINES

S.No	GUIDELINES
1.	E1 Clinical safety for drugs used in long term treatment
2.	E2A-E2F Pharmacovigilance
3.	E3 Clinical study reports
4.	E4 Dose response studies
5.	E5 Ethnic factors
6.	E6 Good clinical practice
7.	E7 Clinical trials in geriatric population
8.	E8 General Consideration for clinical trials
9.	E9 Statistical principles for clinical trials
10.	E10 choice of control group in clinical trials
11.	E11 Clinical trials in paediatric population
12.	E12 Clinical evaluation by therapeutic category
13.	E14 Clinical evaluation
14.	E15 Definitions in pharmacogenetics/ Pharmacogenomics
15.	E17 Multi regional clinical trails
16.	E16 Qualification of genomic biomarkers
17.	E18 Genomic sampling methodologies

Table No : 4- ICH Multidisciplinary Guidelines

S.No	GUIDELINES
1.	M1-MedDRA terminology :(Medical dictionery for regulatory activities)
2.	M2 Electronic standerds
3.	M3 Non clinical safety studies
4.	M4 Common technical document
5.	M5 Data elements and standers for drug dictionaries
6.	M6 Gene therapy
7.	M7 Genotoxic impurities
8.	M8 Electronic common technical document (eCTD)

Figure No: 1 ORGANIZATION CHART OF ICH

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REVIEW ARTICLE

An Overview of Dendrimers

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ABSTRACT

Nanotechnology is a complex subject of study, but its application in medicine will provide considerable benefits in illness treatment. The development of drug delivery systems capable of delivering new bioactive natural compounds to target tissues is one of the new medicines. Nanosystems, such as dendrimers, can successfully administer drugs that are poorly water soluble or have restricted therapeutic indices. As a medication delivery agent, dendrimers are a promising, safe, effective, and selective choice. Due to their unique features, dendrimers dendritic structure design holds a lot of promise, especially for medication delivery. Dendrimers are an excellent delivery vehicle for investigating the impact of polymer size, charge, and composition on biologically important features such lipid bilayer interactions, cytotoxicity, bio-distribution, internalisation, blood plasma retention time, and filtration. These have high solubility, miscibility, and reactivity due to their terminal groups. Dendrimers are monodisperse and have well-defined size, shape, and molecular weight. Dendrimers have gotten a lot of attention in recent years because of their unusual features. Because of their uniform size, water solubility, adjustable surface functionality, and available internal cavities, they are of great relevance in drug delivery applications. Dendrimers are a good carrier for medication delivery because of their features. Dendrimers, often known as modern-day polymers, have far more desirable features than traditional polymers. The role of dendrimers in improved medication delivery is the topic of this review.

Keywords: Dendrimers, Nanotechnology, Dendritic Polymers, Dendrons

INTRODUCTION

Nanotechnology is a new field that investigates materials on a nanoscale size. Nanotechnology has piqued the interest of researchers in the domains of biomedical engineering, pharmaceutical technology, and medicine in recent decades. Nonmaterial's (NM) are structures with less than 100 nm in at least one of their dimensions that have unique physical, chemical, and/or biological properties associated with their nanostructure [1]. Nanomedicine is one of the sub-topics of nanotechnology, with the goal of using nanoformulation to treat and prevent diseases. One of the primary goals of nanotechnology and nanomedicine is to create a good pharmaceutical formulation, that is, to create a safe and effective medication formulation with high quality while increasing the bioavailability of the active pharmaceutical ingredients (API).[2] Due to their different physicochemical and structural features, dendrimers have been emphasised as interesting nanostructures in recent years, and their usefulness as medicinal excipients has been investigated [3]. Dendrimers, among the numerous nanocarriers, are a possible therapeutic tool in biomedical and pharmaceutical science due to their unique physical and chemical features. Dendrimers, a well-established polymeric nanocarrier technology at the time, are capable of transporting both drugs and genetic materials [4]. The linear polymer differs from the dendrimer in that it is made up of a lengthy chain of molecules that crisscross each other like coils.This type of polymer also has significant manufacturing costs and necessitates the use of a skilled crew. However, as nanotechnology advances and knowledge of dendrimers grows, some of these issues are becoming less significant.Because of their simplicity of synthesis, ability to achieve well-defined shapes and sizes, and chemical variety compared to synthetic polymers, dendrimers have gotten a lot of attention for their drug-delivery applications. Dendrimers are highly suited for usage as carrier molecules in drug delivery due to their internal empty space and surface functional groups [5].

DENDRIMERS

The synthesis of "nanocascade spheres" and "starburst dendritic macromolecules" was first described in 1985, ushering in a new class of macromolecules known as dendrimers. Dendrimers, also known as dendritic polymers, are nanoparticles with diameters ranging from 1 to 100 nm that can be employed as drug delivery systems. [6]Dendrimers are a type of three-dimensional, nanoscale hyperbranched synthetic polymer with a symmetrical branched geometry. Dendrimer is derived from the Greek words "dendrons" (tree) and "meros" (part), which are reflective of their unusual "tree-like" branched architecture. Dendrimers are sometimes known as "arboroles" or "cascade" polymers [7].

Properties of Dendrimers [8, 9]

- ✓ Nanoscale sizes are those that are similar in size to crucial bio-building blocks like proteins and DNA.
- ✓ Dendrimers have a spherical and compact structure.
- ✓ Dendrimers are synthesized with care and in a step-by-step process.
- ✓ Dendrimers have a lot of structural flexibility.
- ✓ Dendrimers are monodisperse, highly branching macromolecules with molecular weight, size, and form that can be measured.
- ✓ Numbers of terminal surface groups suitable for drug bioconjugation, signalling, targeting, or biocompatibility.
- ✓ Surfaces having functional groups that can enhance or inhibit transcellular, epithelial, or vascular biopermeability.
- ✓ Small molecule pharmaceuticals, metals, or imaging moieties could be encapsulated in an internal vacuum area. The drug toxicity is reduced and regulated release is made easier by encapsulating it in that vacuum region.
- ✓ Dendrimers have functional groups on the surface for drug conjugation and interior chambers for drug entrapment.
- ✓ Glass temperatures are lower in dendrimers.
- ✓ Positive biocompatibility patterns linked to lower generation anionic or neutral polar terminal surface groups against greater generation neutral polar and cationic surface groups. Most dendrimer surfaces treated with minor

functional groups or polyethylene glycol are non- or low-immunogenic (PEG).

CHARACTERIZATION OF DENDRIMERS

Dendrimers concern both molecular chemistry because of the step by step synthesis approach used during their synthesis and Polymer chemistry due to their repetitive structures that are made up of monomers. Therefore they are usually characterized using analytical techniques from both fields. The chemical composition, morphology, shape, polydispersity, homogeneity, synthesis, conjugation, reaction rates, molecular weight, structural defects, and purity of dendrimers are studied using analytical techniques. They include,

- Spectroscopic methods,
- Scattering techniques,
- Microscopic methods,
- Chromatographic techniques,
- Electrical techniques and
- Rheological/ physical properties analysis.

Spectroscopic Techniques

The amount of radiation generated or absorbed by molecular or atomic species of interest is measured using spectroscopic analytical techniques. Spectroscopic techniques are arguably the most commonly utilised instrument for elucidating molecular structure and determining the quantitative and qualitative properties of both inorganic and organic substances.

Ultraviolet – Visible Spectroscopy

Due to the characteristic absorption maximum or change in the value of lambda max (max), this approach gives confirmation of synthesis as well as surface modification on dendrimers. The functional moieties linked to dendrimer molecules are also detected via UV-visible spectroscopy.

Infra – Red Spectroscopy

The chemical changes at the surface of dendrimers may be routinely analysed using infrared (IR) spectroscopy. As a result, it is an analytical method used to determine synthesis, functional groups, conjugation, and the drug-dendrimer interaction.

Nuclear Magnetic Spectroscopy

The structure and behaviour of molecules in solution may be determined using nuclear magnetic resonance spectroscopy.

Fluorescence spectroscopy

Fluorescence spectroscopy examines fluorescence from a sample and is a form of electromagnetic spectroscopy. Fluorescence spectroscopy is useful for determining the interaction of chemical additives with dendrimers. Fluorescence spectroscopy can be used to determine the size and shape of molecules.

Atomic force microscopy (AFM)

Fluorescence spectroscopy examines fluorescence from a sample and is a form of electromagnetic spectroscopy. Fluorescence spectroscopy is useful for determining the interaction of chemical additives with dendrimers. Fluorescence spectroscopy can be used to determine the size and shape of molecules.

Microscopic Techniques

Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy is commonly used to investigate dendrimer surface topography.

Transmission Electron Microscopy (TEM)

Transmission Electron Microscopy (TEM) is a microscopic method in which a stream of electrons is sent through an ultra-thin object, reacting with it as it passes. This interaction produces a picture, which is enlarged and shown on an imaging device.

Electro analytical Techniques

Low detection limits and a wealth of characterization information describing electrochemically accessible systems such as Stoichiometry and rate of interfacial charge transfer, rate of mass transfer, adsorption extent, and chemical reaction rates and equilibrium constants are all possible with electro analytical techniques.

Electron Paramagnetic Resonance (EPR)

This method is used to investigate chemical entities that have one or more unpaired electrons, such as organic and inorganic free radicals, as well as inorganic complexes containing transition metal ions.

Electrophoresis

This method may be used to determine the purity and homogeneity of a variety of water-soluble dendrimers.

Thermo Gravimetric Analysis (TGA)

Thermo gravimetric analysis determines how much a sample's weight varies when the temperature changes. Differential Thermal Analysis (DTA) indicates whether the changes were exothermic or endothermic in the same way. As a result, in a controlled environment, TGA-DTA monitors heat flow and weight changes in a material as a function of temperature. The thermal stability and weight variations of dendrimer molecules in response to temperature changes were investigated. [10-12]

ADVANTAGES OF DENDRIMERS [12-14]

- ✓ Dendrimers are biodegradable and have low toxicity and immunogenicity.
- ✓ Multiple functional groups are present on the outer surface of dendrimers, which can be used to attach vector devices for targeting to specific sites in the body.
- ✓ Dendrimers may have a higher permeability and retention impact than tiny molecules, allowing them to target tumour cells more efficiently.
- ✓ They can be synthesised and tailored to individual needs. They are great drug delivery systems due to their possible structure, functionality, and dimensions; also, their size is very close to several critical biological polymers and assemblies such as DNA and proteins, which are physiologically optimal.
- ✓ Dendrimers can entrap a wide range of medicines with various functional groups in the interior hollow core or through charge interactions.
- ✓ Dendrimers are less susceptible for reticulum endothelium uptake due to its nanoscopic particle size range (1 - 100 nm).
- ✓ Interferon and tumour necrosis factor, as well as the characteristics of acrylates, may make them naturally anticancer agents.
- ✓ They have better colloidal, biological and shelf-stability.
- ✓ Due to the presence of reactive functional groups on the surface of dendrimers, they have a better/greater targeting efficiency.
- ✓ Dendrimers can be customized as stimuli responsive to release drug.

STRUCTURE OF DENDRIMERS

Generally, dendrimers are globe or ellipsoid shaped, and they consist of three distinct components:

(a) A central core

(b) Repeated branches

(c) Surface functional groups

The central core should be a molecule with at least two reactive functional groups. The repeated branches are organized in a series of radically concentric layers called ‘‘generations.’’ The core of dendrimer is also called ass generation zero or G0.[15]The branching units are described by generation, starting with the central core as generation, which is the intermediate generation that is then transformed into generation 0 (G0) and increases with each successive addition of the branch points (G1, G2, etc); each successive generation exponentially increases the number of terminal groups. As a result, branch points extending from the central core of the G5 dendrimer have four generations. With each generation of the dendrimer, the diameter of the dendritic macromolecules increases linearly, eventually taking on a globular shape. The surface functional groups, which govern the physical properties of dendrimers in the solid state or in aqueous solutions to a large extent, are found on the surface of dendrimer molecules [16].

SYNTHESIS OF DENDRIMERS

PAMAMs were the first synthetic dendrimers, introduced in 1980. Later years saw the development of other dendrimers such as poly (propyleneimine) (PPI) and poly-L-lysine (PLL), glycodendrimers, polyester dendrimers, and Amphiphilic dendrimers. Dendrimers are often made using technologies that allow for structural control at every step of the process. The majority of dendritic structures are created using one of two methods [17].

- Divergent Growth Method
- Convergent Growth Method
- Hypercore And Branched Method
- Double Exponential and Mixed Growth

Divergent Growth Method

The divergent growth approach was the first to be proposed, and it remains the most used today. Tomalia introduced the "divergent approach," in which dendrimer development originates from a core location. This method requires two essential steps,

(i) Coupling of monomers

(ii) Activation of the monomer end-group, to promote the reaction with a new

The divergent processing begins with the activation or alteration of the core and the coupling of the first monomer, resulting in the dendrimer's initial generation. The first generation (G1) is then deprotected or activated in order to react with other branched monomers and create the second generation (G2), and so on. A new generation is obtained when a new layer of branching units is generated. To avoid deficiently created branches in the divergent method, it is critical that each phase of the reaction is fully finished before adding a new generation. At each step of the synthesis, the surface of the dendrimer can be easily functionalized and changed, resulting in the desired medicinal excipients at the end. However, researchers have lately explored the prospect of using the divergent growth method to construct heterogeneously functionalized dendrimers, resulting in dendrimers with a variety of functional groups bonded to the surface [19, 20].

Convergent Growth Method

The convergent process, proposed by Frechet and Hawker in 1989–1990, is an alternate approach for the synthesis of dendrimers. The convergent method, in contrast to the divergent method, creates dendrimers from the surface, rather than the core, of the structure. In order to achieve the appropriate dendritic structure, the convergent growth approach also involves repeating the coupling and activation processes. The surface groups, which are usually two, are first linked to a monomer to form the dendritic segment (dendrons generation zero).[20, 21]The second step involves activating this fragment so that it can combine with other monomers, resulting in the formation of a first-generation Dendron, or dendritic wedge. This synthetic technique can be repeated to produce larger generation dendrons, which can then be linked to a multifunctional core in the last phase to produce the final dendrimer. The convergent synthesis process concludes at the core, when two or more dendrons are fused together to form the dendrimer. Because the coupling process takes place near the focal point of the expanding dendrons, steric inhibition makes the synthesis of big dendrimers (typically above the sixth generation) difficult, resulting in lower yields.Due

to the lesser number of coupling reactions at each growth stage in convergent synthesis than in divergent synthesis, greater structural control is achieved, allowing the synthesis of dendritic products of unrivalled purity. [17, 18, 21].

Hypercore and Branched Method

This process entails the pre-assembly of oligomeric species - oligomers (polymers with a small number of repeating units) that can be joined together to form dendrimers in a short amount of time. The core is reacted with two or more moles of reagent that contains at least two protective branching sites, then the protecting groups are removed. The first generation dendrimers are formed as a result of the released reactive site [17, 20].

Double Exponential and Mixed Growth

Dendrimers are synthesised using both divergent and convergent growth mechanisms in this process. It is the most advanced way of dendrimer synthesis, combining divergent and convergent approaches to produce a triangle known as a 'Dendrimer.' The triangle can be used to repeat the process of growth [17, 19, 21].

MECHANISM OF DRUG DELIVERS THROUGH DENDRIMERS [22, 23]

Drug molecules can be loaded both in the inside of the dendrimers and connected to the surface groups, as previously indicated, due to the well-defined 3D structure and abundance of surface functional groups. Dendrimers can work as drug carriers in two ways: by encapsulating capsules within the dendritic shape or by creating prodrugs by engaging with drugs at their terminal functional groups via electrostatic or covalent interactions.

There are extensively two mechanisms for drug transport:

1. The first one is via in vivo degradation of drug dendrimer covalent bonding which depends on the presence of suitable enzymes or an environment capable of splitting the bonds.
2. The second one is by using releasing the drug because of changes in the physical environment inclusive of pH, temperature.

DENDRIMER DRUG INTERACTIONS

Various interplay mechanisms have been investigated, and they can be categorised into three categories: encapsulations, electrostatic interactions, and covalent conjugations. Dendrimers can act as drug carriers by encapsulating medicines within the dendritic structure or by creating prodrugs by electrostatic or covalently bonding with drugs at their terminal functional groups. The two primary strategies of dendrimer drug delivery are drug encapsulation and dendrimer–drug conjugates/ complexation.

Non-covalent Encapsulation of Drugs / Host - Guest Relation

Dendrimers' ellipsoidal or spherical form, vacant internal cavities, and open architecture allow guest molecules to be directly encapsulated into the macromolecule interior. These empty interior spaces are frequently hydrophobic, making them ideal for interacting with weakly soluble medicines via hydrophobic interactions [24]. Small organic molecules may be incorporated into dendrimers as a result of non-bonding interactions with certain groups within the dendrimer, i.e. simple physical entrapment. The satiric bulk of the dendrimer's exterior is used to encapsulate medicines. Interactions between the dendrimer and the drug, allowing the drug to be trapped within the dendrimer. A method like this might be used to encapsulate medications and administer them in a regulated manner. The utilisation of dendrimers as unimolecular micelles and 'dendritic boxes' for the noncovalent encapsulation of medicinal molecules was the focus of early research of dendrimers as prospective delivery systems.

DNA was complexed with PAMAM dendrimers for gene delivery applications, for example, and hydrophobic medicines and dye molecules were integrated into various dendrimer cores in early research. Dendrimers can be employed as dendritic boxes and unimolecular micelles (dendrimer-drug networks) to incorporate hydrophobic/hydrophilic compounds into their unfilled cavities (nanoscale containers) surrounding the core [25].

Covalent Dendrimer–Drug Conjugates

Alternatively, using the well-defined multivalent feature of dendrimers allows drug molecules to bind to their perimeter, resulting in the creation of complexes. Electrostatic interactions between the drug and the dendrimer molecule or drug conjugation to the dendrimer molecule create the resulting complexes. Various ionizable medicines form compounds with the vast number of ionizable terminal surface groups of dendrimers via electrostatic interactions [26]. The drug is linked to the surface groups of a dendrimer through a covalent connection, either directly or via a linker/spacer, in dendrimer–drug conjugates. Dendrimers have been attached to medicines, antibodies, sugar moieties, and lipids, among other physiologically active compounds. The medication is covalently linked to dendrimers in this scenario, and it is released by the breakage of hydrolytically labile bonds by chemical or enzymatic means. Drug loading can be regulated by integrating degradable connections between the drug and the dendrimer, and drug release may be controlled by changing the generation number of the dendrimer [24]. However, medicines can be covalently conjugated to dendrimers via spacers such as PEG, p-amino benzoic acid, p-aminohippuric acid, and lauryl chains, as well as biodegradable connections like amide or ester bonds.[25]In addition, covalent conjugation allows tissue targeting and controlled delivery as the drug–dendrimer conjugates diffuse slower than the free drug in the body and might be absorbed in specific interfaces [24].

FUTURE PROSPECT

Dendrimer drug delivery methods are becoming more popular as a viable option for bioactives such as medicines and genes. They serve as a platform for attaching medicines or genes and releasing them through a variety of methods. Dendrimer drug delivery is successful only if specific manufacturing and biological aspects are taken into account. Dendrimer technology's utility will be bolstered in the future years as commercial applications grow. Dendrimers have been researched for use in medication administration for a variety of applications, including oral, transdermal, ophthalmic, nasal, parental and gene delivery, ocular, pulmonary, intranasal, and intravaginal for the treatment of life-threatening illnesses. The potential for dendrimers to be used in nanomedicine in the future is greatly reliant on the productivity of the final component characteristics. Thus, in order to progress the usage of dendrimer-based products into clinical trials, it is critical to create well-defined dendrimers that are multifunctional.

CONCLUSION

Dendrimers may be an effective technique for improving the delivery of such difficult-to-absorb drugs. They provide a platform for the attachment of drugs or genes and their release through several mechanisms such as physical encapsulation, electrostatic interaction and covalent conjugation. The high level of control over the architecture of dendrimer, their shape, branching length and density, their surface functionality and interior void space (porosity) and so on. These properties construct the dendrimers a smart choice for drug delivery application and improve the solubility of poorly soluble drug and also increase stability of drug.The role of dendrimers in enhanced medication delivery is briefly discussed. Dendrimers have a wide range of applications, including gene transfection and diagnostics, in addition to medication delivery. One of the most essential factors in the effective application of dendrimers is their pharmacokinetic characteristic. The goal of this project was to figure out how to prepare and study the characteristics of a new class of macro and micro molecules. Despite the fact that dendrimers have been discovered for over two decades, the multi-step synthesis still takes a lot of time and effort. The majority of drugs are class 2 drugs with low solubility, which is enhanced by dendrimer drug delivery by entrapping the molecule in the dendrimer's core.

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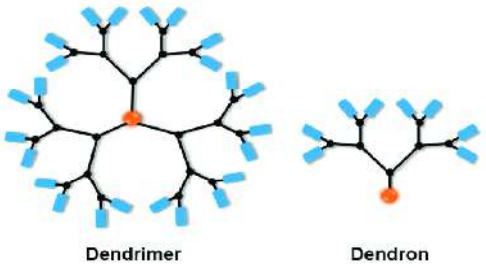

sssFig. I: Dendrimers

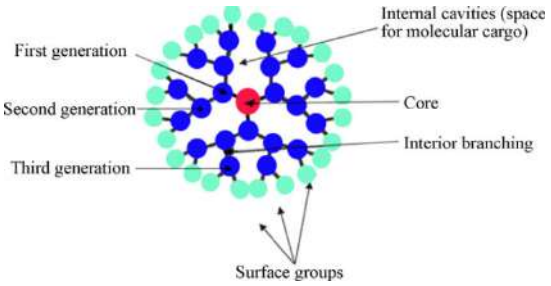

Fig. II: Structure of Dendrimer

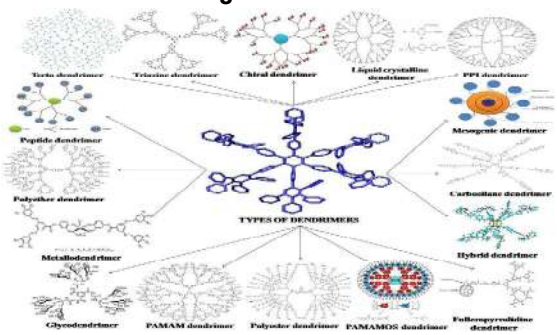

Fig. III: Types of Dendrimers

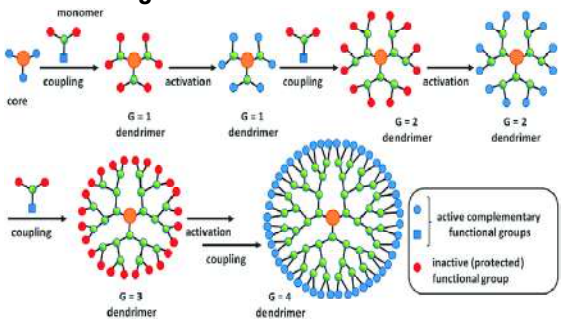

Fig. IV: Divergent Growth Method

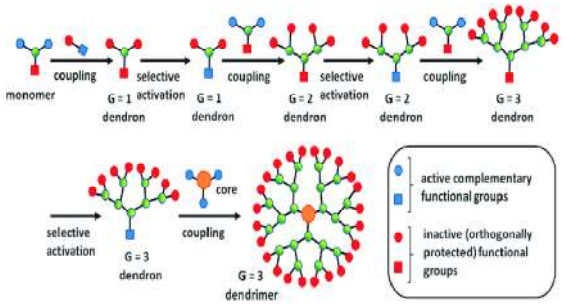

Fig. V: Convergent Growth Method

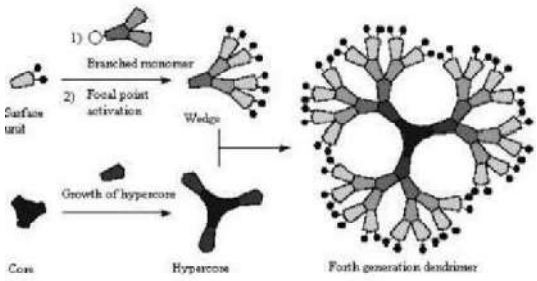

Fig. VI: Hypercore and Branched Method

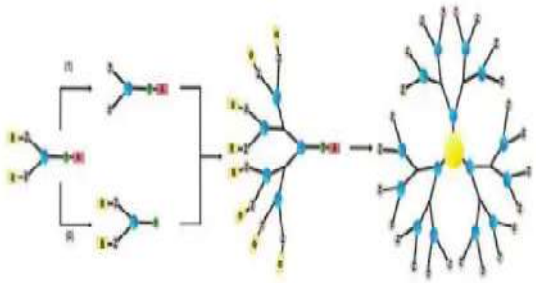

Fig. VII: Double Exponential and Mixed Growth

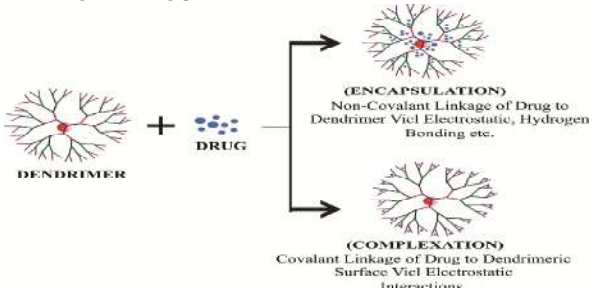

Fig. VIII: Drug to Dendrimer Interactions

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RESEARCH ARTICLE

The GC MS Study of One Ayurvedic Medicine Pippalyasavam

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ABSTRACT

In order to known the molecules present in one Ayurvedic medicine, Pipplayasavam, it was subjected to GC MS analysis. This medicine is prescribed for ailments such asbowel diseases, anaemia, piles, cough, intestinal gas and abdominal distension, loss of appetite, anorexia. The medicine was procured from standard Ayurvedic vendor at Chennai and was processed as per protocol before GC MS analysis. The GC MS profile indicated the presence of some medicinally important molecules such as Eugenol, Undecanoic acid, 10-methyl-, methyl ester, Methyl tetradecanoate, Hexadecanoic acid, methyl ester, 12, 15-Octadecadienoic acid, methyl ester, Methyl stearate, n-Propyl 9,12-octadecadienoate, Oleic Acid, Octadecanoic acid, 17-methyl-, methyl ester, Squalene, i-Propyl 5,8,11,14,17-eicosapentaenoate, .beta.-Sitosterol etc. which could directly or indirectly contribute to the action of Pipplyasavam. It is concluded that there could be some direct or indirect role of the molecules present in Pipplyasavam in curing digestive disorders.

Keywords: Pipplyasavam, GC MS, Ayurvedic,anaemia, anorexia, Eugenol, Squalene

INTRODUCTION

Ayurvedic and other forms of complementary and alternative medicinal practices are in vogue since time immemorial. The need to standardize these medicines in the light of modern medical practices is immensely required. The present study is one more attempt in this regard by these workers who have embarked upon establishing the efficacy of Ayurvedic medicines and other complementary and alternative medicines. [1-29]This work reports the GC MS analysis results of one Ayurvedic medicine, Pippalyasavam, which is prescribed for the treatment of bowel diseases, anaemia, piles, cough, intestinal gas, and abdominal distension, loss of appetite, anorexia, and fevers. It acts on the stomach and increases the secretion of gastric juices. It also acts on the liver and stimulates bile secretion into the intestine. Thus, it improves appetite and digestion. It is also detoxifying in its action, which reduces the formation and accumulation of Aama (toxins) in the body. It is best for people having Kapha and Vata dominance in their symptoms.

Ingredients: one part each of Pippali– *Piper longum*, Kali Mirch – *Piper nigrum*, Chavya – *Piper chaba*, Turmeric (*Curcuma longa*), Chitrak – *Plumbago zeylanica*, Nagarmotha – *Cyperus rotundus*, Vaividanga – *Embelia ribes*, Supari – *Areca catechu*, Lodhra – *Symplocos racemosa*, Patha – *Cissampelos pareira*, Amla (*Phyllanthus embelica*), Ushira – *Vetiveria zizanioides*, Safed Chandan – *Santalum album*, Kushta – *Saussurea lappa*, Laung – *Syzygium aromaticum,* Tagara (*Valleriana wallichi*), Jatamansi (*Nardostachys jatamansi*), Dalchini – *Cinnamomum zeylanicum*, Cardamom (*Elletaria cardamomum*), Indian bay leaves (*Cinnamomom tamala*), Priyangu – *Callicarpa macrophylla* (flowers) and Nagakesara (*Mesua ferrea***)** are mixed with 1024 parts of water, 600 parts of Jaggery, 20 parts of Dhataki (*Woodfordica fruticosa*) flowers, and 120 parts of grapes (*Vitis vinifera*) and kept tightly packed in asava/arishat vessel for one month. After that the fluid is filtered as bottled as medicine. 10 to 30 ml of Pippalyasavam is taken with equal amount of water twice a day after food or as prescribed by the physician. The reference for this medicine is from Sarnagadhar Samhita Madhyama Khanda 28 to 33.

MATERIALS AND METHODS

Pippalyasavam was obtained from standard Ayurvedic vendor at Chennai and was subjected to GC MS analysis by standard procedure. The compounds are identified by GC-MS Library (NIST & WILEY).

RESULTS AND DISCUSSION

The GC MS profile of Pippalyasavam is represented in Figure 1. Table1 indicates the retentions time, types of possible compound, their molecular formulae, molecular mass, percentage peak area and their medicinal roles of each compound as shown in the GC MS profile of Pippalyasavam. The identification of metabolites was accomplished by comparison of retention time and fragmentation pattern with mass spectra in the NIST spectral library stored in the computer software (version 1.10 beta, Shimadzu) of the GC-MS along with the possible pharmaceutical roles of each bio molecule as per Dr. Duke's Phytochemical and ethnobotanical data base (National Agriculture Library, USA) and others as shown in Table 1 [30]. Table 1 indicates the presence of important biomolecules such as Eugenol, Undecanoic acid, 10-methyl-, methyl ester, Methyl tetradecanoate, Hexadecanoic acid, methyl ester, 12, 15-Octadecadienoic acid, methyl ester, Methyl stearate, n-Propyl 9,12-octadecadienoate, Oleic Acid, Octadecanoic acid, 17-methyl-, methyl ester, Squalene, i-Propyl 5,8,11,14,17-eicosapentaenoate, .beta.-Sitosterol etc. which have multiple roles that could support the medicinal role of Pipplayasavam.

CONCLUSION

The presence of medicinally important molecules could assist in the function of Pippalasavam towards curing gastric ailments. It will be of interest to understand the medicinal roles of those molecules which are not known.

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Table1. Indicates the retentions time, types of possible compound, their molecular formulae, molecular mass, percentage peak area and their medicinal roles of each compound as shown in the GC MS profile of Pippalyasavam.

Sl. No	Retention Time	Compound Name	Mol. Formula	Mol. Weight	% Peak Area	Possible medical Role
1	6.225	3-Phenylpropanol	C9H12O	136.1	3.22	Not known
2	6.526	Coumarin, 3,4-dihydro-4,4,7-trimethyl-	C12H14O2	190.1	1.39	Not known
3	7.1	5-(Hydroxymethyl)-2-(dimethoxymethyl)furan	C8H12O4	172.1	23.21	Not known
4	7.84	Eugenol	C10H12O2	164.1	7.21	Eugenol has many medicinal properties such as antifungal, antioxidant, anticonvulsant, local anaesthetic, anti-stress, bacteriostatic, bactericidal, anti-carcinogenic, depresses activity of central nervous system, anti-radiation, antiviral, induces apoptosis in melanoma cells and HL-60 leukemia cells.[31-32]
5	8.59	Benzene, 1,1'-(1-methylethylidene) bis[4- methoxy-	C17H20O2	256.1	1.24	Not known

6	9.771	Phenol, 3,5-bis(1,1-dimethylethyl)-	C14H22O	206.2	0.85	Not known
7	9.955	Undecanoic acid, 10-methyl-, methyl ester	C13H26O2	214.2	1.43	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
8	10.396	Estra-1,3,5(10)-trien-17.beta.-ol	C18H24O	256.2	1.28	Not known
9	12.18	Methyl tetradecanoate	C15H30O2	242.2	1.38	Catechol-O-Methyl-Transferase-Inhibitor, Methyltransferase-Inhibitor, Methyl-Donor, Methyl-Guanidine-Inhibitor
10	14.211	Hexadecanoic acid, methyl ester	C17H34O2	270.3	5.02	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
11	15.739	12,15-Octadecadienoic acid, methyl ester	C19H34O2	294.3	2.54	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
12	15.807	11-Octadecenoic acid, methyl ester	C19H36O2	296.3	8.37	Catechol-O-methyl-Transferase Inhibitor, methyl donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
13	16.069	Methyl stearate	C19H38O2	298.3	2.21	Catechol-O-methyl-Transferase Inhibitor, methyl donar, Methyl Guanidine Inhibitor
14	16.335	n-Propyl 9,12-octadecadienoate	C21H38O2	322.3	6.18	Anaphylactic, Antitumor, Arylamine-N-Acetyltransferase-Inhibitor. Decreases Norepinephrine Production, Down regulates nuclear and cytosol androgen reuptake, GABA-nergic, Increases Natural Killer (NK) Cell Activity, Inhibits Production of Tumor Necrosis FactorAntitumor,

						anticancer, myoneuro-stimulant, decreases norepinephrine production, NADH-Oxidase inhibitor, NADH-Ubiquinone Oxidoreductase inhibitor
15	16.399	Ethyl Oleate	C20H38O2	310.3	5.90	Not known
16	16.462	Oleic Acid	C18H34O2	282.3	0.75	Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
17	16.664	Octadecanoic acid, 17-methyl-, methyl ester	C20H40O2	312.3	0.91	Catechol-O-methyl-Transferase Inhibitor, methyl donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
18	18.32	7-Methyl-Z-tetradecen-1-ol acetate	C17H32O2	268.2	0.81	Oligosaccharide provider
19	18.801	Octasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13,15,15-hexadecamethyl-	C16H50O7Si8	578.2	1.19	Not known
20	19.412	Bis(2-ethylhexyl) phthalate	C24H38O4	390.3	2.14	Not known
21	20.625	Octadecane, 3-ethyl-5-(2-ethylbutyl)-	C26H54	366.4	0.89	Not known
22	20.96	Heptasiloxane, hexadecamethyl-	C16H48O6Si7	532.2	10.60	Not known
23	21.472	Squalene	C30H50	410.4	7.04	Monooxygenase inhibitor, biochemical precursor ofsteroid synthesis, natural moisturizer, used in cosmetics
24	22.011	Octatriacontylpentafluoropropionate	C41H77F5O2	696.6	1.11	Not known
25	22.434	Geranylisovalerate	C15H26O2	238.2	0.80	Not known
26	22.473	Octadecanoic acid, 4-hydroxy-, methyl ester	C19H38O3	314.3	0.74	17 beta hydroxysteroid dehydrogenase inhibitor, Aryl hydrocarbon hydroxylase inhibitor, testosterone hydroxylase inducer, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
27	23.145	i-Propyl 5,8,11,14,17-eicosapentaenoate	C23H36O2	344.3	0.75	Ionotrpoic, 11B-HSD inhibitor, 5 alpha reductase inhibitor, HIF1 alpha inhibitor, Alpha amylase inhibitor, IkappaB-alpha

						alpha phosphorylation inhibitor, Interlukine- 1 alpha inhibitor, Testosterone 5 alpha reductase inhibitor, 12 Lypoxygease inhibitor, 17 beta hydroxysteroid dehydrogenase inhibitor, 5 HETE inhibitor, 5 HT inhibitor, 8 HETE inhibitor, ACE inhibitor, Acetyl CoA carboxylase inhibitor
28	24.375	.beta.-Sitosterol	C29H50O	414.4	0.85	17 beta hydroxysteroid dehydrogenase inhibitor, Antiamyloid beta, Anti TGF beta, Beta receptor agonist, Beta-adrenergic receptor blocker, beta blocker, beta galactosidase inhibitor, beta glucuronidase inhibitor, ER beta binder

Qualitative Compound Report

Data File	200520019.D	**Sample Name**	Pippalyasavam
Sample Type		**Position**	20
Acq Method	GC Screening Method.M	**Acquired Time**	22-05-2020 AM 08:14:38
Comment			

User Chromatogram

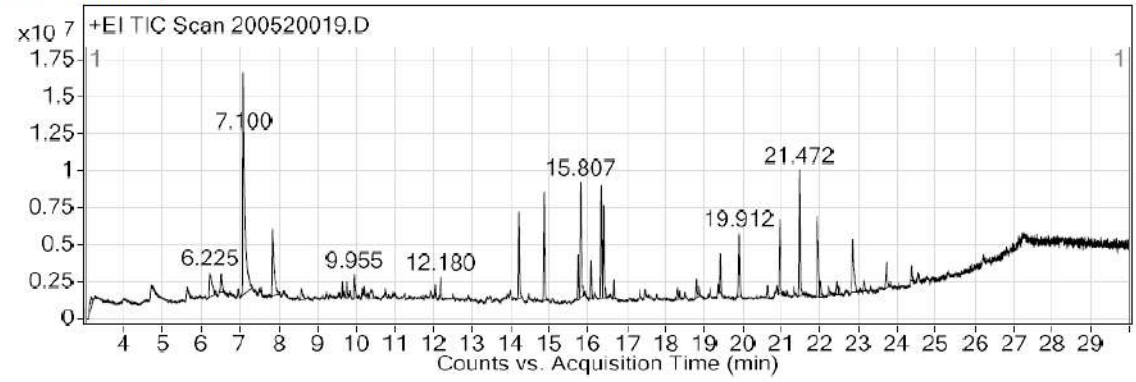

Figure 1. Depicts the GC MS profile of Pipplayasavam

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RESEARCH ARTICLE

Comparative Study of Acid-Neutralizing Capacity of Different Brands of Antacid Tablets and Suspensions Available in Guwahati, India

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ABSTRACT

The study aims to evaluate the acid-neutralizing capacity of three tablets and four suspensions which are commercially available in local pharmacies of Guwahati, Assam and are widely used as antacids. The individual samples were purchased and the tablet samples were crushed, powdered and weighed. Before using the tablet and suspension samples for analysis they were kept at room temperature. 0.5g of each tablet sample were taken for titration and was dissolved in 20ml of 0.1M hydrochloric acid and the resultant solution were titrated against 0.1M NaOH. For suspensions, 1ml of the sample was taken, dissolved in 20ml 0.1M hydrochloric acid and was titrated against 0.1M NaOH. Titre values were recorded for all the samples. Analysis of the samples showed that among Tablets Gelusil was found to have the highest ANC whereas among suspensions Digene was found they have the highest ANC.

Keywords: Antacids, Tablets, Suspensions, Acid-Neutralizing capacity, Titration

INTRODUCTION

Antacids are basic drugs that are used worldwide as over the counter (OTC) drugs or prescribed medications. The antacids are acid neutralizers and it is used in the treatment of peptic ulcer, heartburn, dyspepsia, gastroesophageal reflux disease (GERD) etc. Antacid neutralizes the hydrochloric acid in the stomach and increases the pH of the gastric contents [1,2]. Antacids can also rise the tone of the lower esophageal sphincter and thereby reduces the activity of GERD and gastric contents in the lower esophagus [3]. In the antacid formulation, hydroxide is mainly used and it is the most common base and other bases such as trisilicate, carbonate and bicarbonate are also used. Antacids therapeutic efficacy and adverse effect is mainly dependent on the metallic ion and also the base in which the metallic ion is combined. Aluminum, magnesium or sodium are the most common base with which metallic ion is combined [4]. The neutralization of acid and its rapid action is the main principle characteristics of an antacid [5].(Figure 1) Antacids are classified into two categories: systemic antacid and non-systemic antacids. Systemic antacids are drugs that are absorbed systemically and may cause a rise in pH to 7. Some examples of systemic

antacids are sodium bicarbonate and sodium citrate. Sodium bicarbonate is most commonly used in comparison to other systemic antacids. Sodium bicarbonate is white in color and is an antacid that gets absorbed completely in the gastric acid. Sodium bicarbonate is an effective as well as a rapidly acting antacid. When the sodium bicarbonate reacts with gastric acid, it will liberate Carbon dioxide (CO2) during the acid neutralization reaction and thus, it will give relief from abdominal discomfort.

The main adverse effect of sodium bicarbonate is systemic alkalosis. The other adverse effects of systemic antacids are nausea, belching, flatulence, fullness and also the rupture of the peptic ulcer. On the other hand, non-systemic antacids are drugs that are insoluble and get poorly absorbed. After absorption, these drugs react in the stomach and it will form chloride salt. Examples of some non-systemic antacids are magnesium hydroxide, magnesium trisilicate, aluminum hydroxide, magaldrate and calcium carbonate. Among all the non-systemic antacids the aluminum hydroxide is mainly used. In the stomach, the aluminum hydroxide reacts with the gastric acid and it will form aluminum chloride. The main advantage of aluminum hydroxide is that it has both astringent and demulcent property and for this property, the aluminum hydroxide will form a protective coating that covers the ulcer crater. Aluminum hydroxide also absorbs toxins, gases and bacteria. The main adverse effect of aluminum hydroxide is constipation. The other adverse effects are osteomalacia, encephalopathy and osteodystrophy [6]. Magnesium hydroxide is also most commonly used as a non-systemic antacid. Generally, it is available as milk of magnesia which contains magnesium hydroxide in the amount of 7 to 8.5%. The magnesium hydroxide is more palatable than the other magnesium formulations. Diarrhea is the major side effect of magnesium hydroxide [7]. The non-systemic antacids having no systemic absorption because the salt form of non-systemic antacid when combined with gastric acid, it forms an original base and thus, it will be excreted from the feces [8]. Simethicone and dimethicone are also used in the formulation of antacids [9]. The present study aims to find the best antacids available commercially in Guwahati, Assam in form of tablets and suspensions in terms of their Acid-neutralizing capacities.

MATERIALS AND METHODS

Materials

Reagents

0.1M Sodium hydroxide (NaOH), 0.1M Hydrochloric acid (HCl), Distilled water and indicator Thymol blue were used.

Glass wares

Volumetric flask, measuring cylinder, pipette, burette, beaker, conical flask, stirrer, mortar and pestle and spatula were used in this experiment.

Sample Information

For this experiment, we purchased 3 different brands of antacid tablets and 5 different brands of antacid suspensions from local pharmacies located in Guwahati city of Assam, India. The table for antacid formulations and their composition are given in Table 1.

Methodology

The experiment which we had performed is mainly based on an acid-base neutralization reaction. This study mainly lies between the sample of the antacid and the amount of acid which is required for the neutralization of the antacid.

Sample Preparation

0.1M Sodium Hydroxide solution: For the preparation of NaOH (0.1M), 0.8 gm of sodium hydroxide pellet was weighed and transferred to a dry beaker (100 ml). After that, 100 ml of distilled water was poured into the beaker and stirred gently to dissolved the sodium hydroxide pellets and the beaker has been labelled as 0.1M.

0.1M Potassium Hydrogen Phthalate solution: For the preparation of potassium hydrogen phthalate (0.1M), 2.04 g of potassium hydrogen phthalate (KHP) was taken in a volumetric flask (100 ml) and a little amount of distilled water was added to the conical flask and stirred gently to dissolved the KHP. After that, the volume was made up to 100 ml by adding distilled water.

0.1M Hydrochloric Acid solution: For the preparation of HCl (0.1M), 0.84 ml of HCl was taken by using a pipette and transferred to a volumetric flask (100 ml). After that, distilled water was added to the volumetric flask and made up to 100 ml and the flask has been labelled as 0.1M.

Antacid sample preparation (Tablets and Suspensions)

An antacid tablet was taken from the strip of tablet and the weight of the tablet was also taken. Then, the tablet was crushed by using mortar and pestle. After crushing, 0.5 g powder of the tablet was taken in a conical flask. After that, 20 ml of prepared HCl solution was added to the conical flask and the flask was kept aside to dissolve the powder in HCl.On the other hand, 1 ml of antacid suspension was taken in another conical flask by using a measuring cylinder and 20 ml of prepared HCl solution was added to the flask. After that, the flask was kept aside to dissolved the suspension in HCl.

Titration

For the titration, one burette was taken and washed with distilled water. The burette was filled with prepared sodium hydroxide (0.1M) solution and after filling the burette, one white paper was placed on the base of the burette. After that, the sample of antacid tablet and suspension was taken in a conical flask (250 ml) and three drops of thymol blue indicator was added to the solution by using a pipette. After adding the indicator, the solution became pale yellow or orange and the sample solutions were titrated against the prepared sodium hydroxide solution (0.1M) which was taken in the burette. The process was stopped at the point where the color of the solutions in the conical flask changes to a purplish color. The determination of the acid-neutralizing capacity of both the samples (tablet and suspension) was calculated.

Standardization of NaOH

For the standardization of NaOH, 20 ml of prepared KHP solution (0.1M) was taken in a conical flask. After those three drops of phenolphthalein indicator was added to the conical flask and titrated against NaOH (0.1M) solution. In the end, the colorless solution of the conical flask changes to pink color.

Standardization of HCl

For the standardization of HCl, 20 ml of prepared HCl (0.1M) was taken in a conical flask. After that, three drops of phenolphthalein indicator were added to the conical flask and titrated with prepared NaOH (0.1M) solution. When the drops of NaOH falls on the solution of the conical flask a pink color will come and instantly disappeared. In the end, the color of the solution in the conical flask changes to pink color.

The following formulas are used in the determination of Acid-Neutralizing Capacity of tablets and suspensions [10]:

$$\text{Total amount of HCl (mole) used} = \frac{\text{Molarity of HCl x Volume of HCl}}{1000}$$

$$\text{Amount of HCl neutralized by NaOH} = \frac{\text{Molarity of HCl x Titre value}}{1000}$$

$$\text{The Excess HCl neutralized by antacid} = M_{(HCl)} - M_{(HCl\text{neutralized by NaOH})}$$

The excess HCl neutralized by a molar mass unit of antacid can be determined by the multiplication of excess HCl neutralized by antacid with the molar mass of antacid. Most antacid sample contains same active ingredients i.e., magnesium hydroxide and aluminum hydroxide, e.g., Gelusil, Polycrol, PAN-MPS, Diovol, Digene contains magnesium and aluminum hydroxide.

The percentage (%) of acid neutralized by antacid can be determined by the following equation:

% Of Excess HCl neutralized =

$$\frac{Amount\ of Excess\ HCl\ neutralized\ per\ molar\ mass\ unit of antacid}{mass\ of antacid} x\ 100$$

RESULTS AND DISCUSSION

The analysis of different brands of antacid tablets and suspensions were carried out. Antacid neutralizes acid but all antacid formulations do not have the same capacity to neutralize the acid. The result from this study says that Digene showed a lower titre value i.e.,12.6, while Diovol showed a higher titre value i.e., 15.1. This result indicates that Digene with a lower titre value holds the highest acid-neutralizing capacity, while Diovol with the higher titre value shows the lowest acid-neutralizing capacity as compared to the other tablets. In the case of suspension, Digene showed the lower titre value i.e., 48.5 and PAN-MPS holds the higher titre value i.e., 55.6. Digene neutralized the acid in a short time and because of this lower titre value, Digene shows the highest acid-neutralizing capacity and the higher titre value of PAN-MPS showed the lowest acid-neutralizing capacity than the rest of the suspensions. After the observations, it was found that less amount of Digene (tablet) and Digene (suspension) was needed to neutralize excess acid in comparison to the other antacids. (Table 2, Figure 2, Figure 3)

CONCLUSION

All we know that antacids are the drugs that are used in the treatment of peptic ulcers, gastric acidity, GERD etc. Antacid neutralizes excess gastric acid in the stomach as well as it increases the pH of the gastric contents. People take different antacid formulations to relieve heartburn, acidity etc. but it is important to know that which antacids are most effective as well as fast-acting. The results of this present experimental work clearly suggested that in tablet formulations Digene has the maximum acid-neutralizing capacity i.e., 69% and in suspensions again Digene has the maximum acid-neutralizing capacity i.e., 86%. The patients who are suffering from dyspepsia, peptic ulcer, heartburn and other stomach related problems will be benefited from these antacids.

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Table 1. Composition of Antacids used in the Acid-Neutralizing capacity study

Sl.no	Name of formulations	Composition	Quantity	Price
1	**Gelusil® tablet**	Activated dimethicone IP Magnesium hydroxide IP Dried aluminum hydroxide IP Magnesium aluminum silicate hydrate	50 mg 250 mg 250 mg 50 mg	Rs.18.10 for 15 tablets
2	**Diovol™ tablet**	Dried aluminum hydroxide IP Magnesium hydroxide IP Magnesium aluminum silicate hydrate Activated dimethicone IP	50 mg 250 mg 250 mg 50 mg	Rs.21.95 for 20 tablets
3	**Digene® tablet**	Dried aluminum hydroxide gel IP Magnesium aluminum silicate hydrate Magnesium hydroxide IP Simethicone IP	300 mg 50 mg 25 mg 25 mg	Rs.18.15 for 15 tablets
4	**Diovol™ suspension**	Dried aluminum hydroxide IP Magnesium hydroxide IP Activated dimethicone IP Sorbitol solution IP	250 mg 250 mg 50 mg 1.25g	Rs. 125
5	**PAN MPS® suspension**	Aluminum hydroxide paste equivalent to dried aluminum	250 mg	Rs. 92

		hydroxide IP Magnesium hydroxide paste equivalent to magnesium hydroxide IP Activated dimethicone IP	250 mg 50 mg	
6	**Digene® suspension**	Magnesium hydroxide IP Simethicone IP Sodium carboxy methyl cellulose IP Dried aluminum hydroxide gel IP	185 mg 50 mg 100 mg 830 mg	Rs. 119
7	**Polycrol® suspension**	Activated dimethicone IP Magnesium hydroxide IP Aluminum hydroxide gel IP Sorbitol (70%) IP	125 mg 100 mg 5 g 645 mg	Rs. 115

Table 2. Result of analysis of Different Antacid Samples

	Diovol (tablet)	Gelusil (tablet)	Digene (tablet)	Digene (suspension)	Polycrol (suspension)	Diovol (suspension)	PAN-MPS (suspension)
Titre value (ml)	15.1	11.1	12.6	48.5	51.3	53.7	55.6
Total amount of HCl used (mol) x 10^{-3}	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Amount of HCl neutralized by NaOH (mol.) x 10^{-3}	1.51	1.11	1.20	4.85	5.13	5.37	5.56
Excess HCl neutralized by Antacid (mol.) x 10^{-4}	18.4	18.8	18.7	15.15	14.87	14.63	14.44
Mass of Antacid used (g)/(ml)	0.5	0.5	0.5	1	1	1	1
Molar mass of the antacid (g/mol)	136	310	136	310	136	136	136

Excess HCl neutralized by a molar mass unit of Antacid (g/mol)	0.244	0.328	0.255	0.865	0.814	0.781	0.739
NC or % of ExcessHClneutralized	48%	65%	51%	86%	81%	78%	73%

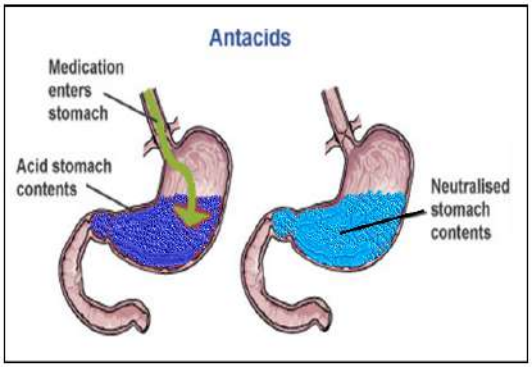

Figure 1.Representation of Antacids action in Stomach

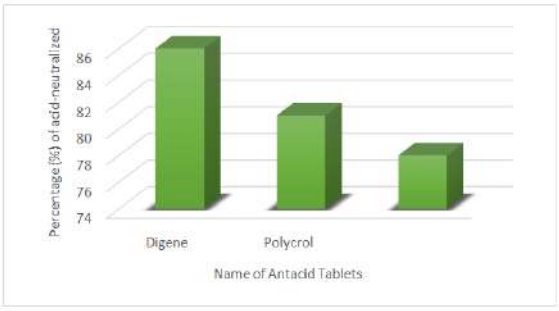

Figure 2. Acid neutralizing value of antacid tablets

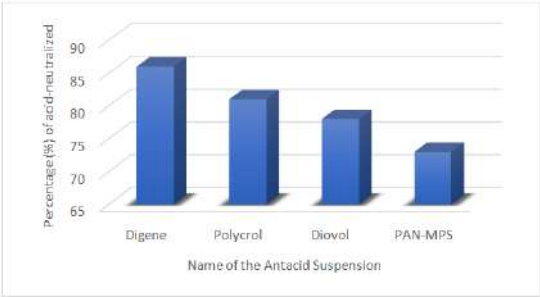

Figure 3. Acid neutralizing value of antacid suspensions

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REVIEW ARTICLE

A Review on Non Clinical Drug Development

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ABSTRACT

The non-clinical development phase mainly targets to identify which candidate remedy has the first-rate chance of success, verify its safety, and constructs table medical foundations earlier than transition to the clinical development phase. The studies in non-clinical development are performed by *In silico,* In vitro and In vivo studies. The objectives of once a candidate compound are identified, the non-scientific improvement ought to begin answering the subsequent questions, and solutions will come from particular research. Data are supplied in keeping with the Common Technical Document (CTD) layout as described via way of means of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).The CTD is organized into five modules. Investigational new drug (IND), New drug application (NDA), Abbreviated new drug application (ANDA), investigation of medicinal products dossier (IMPD), investigator's brochure (IB) are methods should be performed in the non clinical drug development. Non-clinical research have to be strictly accomplished according with appropriate institutional medical practices and additionally using GLP necessities (quintessential for the request and approval of a IND) in an effort to make certain the pleasant, reproducibility and reliability of non-clinical data, in an effort to help the early clinical research contributing to the a success improvement of a new drug.

Keywords: Non clinical, research, clinical trials, phase, regulatory.

INTRODUCTION

The non-clinical development phase mainly targets to identify which candidate remedy has the first-rate chance of success, verify its safety, and construct stable medical foundations earlier than transition to the clinical development phase. Also, for the duration of the non-clinical development phase, the candidate compound ought to meet non-clinical objectives, which includes defining the belongings rights and making sufficient medicinal product to be had for medical trials. The non-clinical development of drugs is complicated and regulatory-driven. Non-clinical refers to research now no longer associated to, involving, or concerned with the direct remark and remedy of residing patients.

The formal idea of ''Good Laboratory Practice'' (GLP) was released in the USA, during the 1970s, way to steady discussions approximately the robustness of the non- scientific protection facts submitted to the FDA for New Drug Applications (NDA). At that time, inspections achieved in the laboratories, revealed: (4)

- Inadequate making plans and flaws in research execution.
- Insufficient documentation of methods, outcomes or even fraudulent facts which aren't documented.
- Use of hematological facts from different research as a manage group.

The studies in non-clinical development are performed by (5)

- *In silico*
- *In vitro*
- *In vivo*

***In silico* studies**

In silico are achieved on pc or throughpc simulation. For example, predicting the toxicology profile of a product the use of its chemical shape from information-primarily based totally approaches.

***In vitro* studies**

In vitro is way in the glass. It is outline as acting a process in managed surroundings outdoor of a residing organism. For example, use of hepatocyte a cell from the liver cultures for metabolism research.

***In vivo* studies**

In vivo research is way in residing. It is experimentation the use of a whole, residing organism rather than tissues or cells, i.e. animals, human beings or plants.

Objectives of non clinical drug development: (6,7)

Once a candidate compound is identified, the non-scientific improvement ought to begin answering the subsequent questions, and solutions will come from particular assessments/research:

- Does it϶acts? → efficacy evaluation
- How will϶or not it's introduced and the way will frame react? → profiling
- Is it϶secure? → toxicology/protection
- Is the manufacture϶feasible and controllable?

Non-clinical development works can keep in the route of lifestyles-cycle product, despite the fact that the earlier the ones questions are answered, the less difficult it's miles to understand the profile of the affected character who will benefit most.

Project control (7)

The non-clinical development programme is complicated and calls for stable challenge control and communication abilities in using multidisciplinary teams. The challenge group desires to apprehend the meant scientific plan so one can outline the non-scientific plan and associated sports. The profile gives a framework to execute the non-clinical development strategy, defining goals, risk, liabilities, metrics and Go/No-Go decision-making. Profile implementation facilitates to maintain the focal point of the challenge on key product criteria, to assist 'Go/No-Go' decisions in a well timed way and to lessen the general challenge risk (i.e., persisted improvement of a non-beneficial product).

NON-CLINICAL REGULATORY GUIDELINES: (8,9,10)

There are many players worried in the improvement of medicines, and every agency or group follows their personal set of rules. For instance, organizations have their Standard Operating Procedures (SOP). In addition to Good Clinical Practice provisions, recommendations may be consulted on the European Medicines Agency (EMA) website.

- They are both preferred and extra particular addressing medical and technical aspects (e.g. particular to required toxicology research).
- They ought to be strictly accompanied for any new advertising authorization utility; any deviation ought to be justified.

Data are supplied in keeping with the Common Technical Document (CTD) layout as described via way of means of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The settlement to collect all of the Quality, Safety, and Efficacy facts on this not unusual place lay out (the CTD) has revolutionized the regulatory assessment method, and has caused harmonized digital submissions that, in turn, permit the implementation of good review practices. For industry, it has removed the want to reformat the facts for submission to the one-of-a-kind regulatory government (the ICH brings collectively the regulatory government and pharmaceutical industry of Europe, Japan, and America to speak about medical and technical elements of medicines registration).

Non-clinical development in CTD modules (9,10)

The CTD is organized into 5 modules (see determine above). In July 2003, the CTD have become the necessary layout for brand new advertising and marketing authorization programs within side the EU and Japan, and the strongly encouraged layout of preference for New Drug Applications (NDA) submitted to the US Food and Drug Administration (FDA).

INVESTIGATIONAL NEW DRUG (IND) (11,12,13)

Investigational New Drug is described below 21 CFR 312.3(b) as a new drug or organic drug this is utilized in scientific research'. The time period additionally consists of an organic product utilized in-vitro for diagnostic purposes. After pre-scientific investigations while the brand new molecule has been screened for pharmacological hobby and acute toxicity capability in animals the sponsor calls for permission from FDA for its scientific trials in human beings. The sponsor submits the utility for behavior of human scientific trials referred to as Investigational New Drug (IND) utility to FDA or DCGI .Once IND utility is submitted , the sponsor ought to look ahead to 30 days earlier than beginning any scientific trial. Clinical trials in human beings can start most effective after IND is reviewed through the FDA and a nearby institutional evaluate board (IRB).IRBs approve scientific trial protocol, knowledgeable consent of all contributors and suitable steps to save you topics from harm.

TYPES OF INDs

A. COMMERCIAL INDs

These are packages which might be submitted commonly through the organizations to achieve advertising acclaim for a brand new product.

B. NONCOMMERCIAL (Research)INDs

These INDs are filed for noncommercial studies.

These are:

1) Investigator's IND

It is submitted through a doctor who each initiates and conducts a research and who additionally administers and dispenses the IP. A doctor may post a studies IND to recommend analyzing an unapproved drug or an authorized drug for brand spanking new warning signs or in new affected person population.

2) Emergency Use IND

This IND lets in FDA to permit the usage of an experimental drug in an emergency state of affairs that doesn't permit submission of an IND according with 21 CFR Sec312.23 or Sec 312.34. It also can be used for sufferers who do now no longer meet the standards of a current have a look at protocol or if an authorized have a look at protocol does now no longer exist.

3) Treatment IND

It is also referred to as Expanded Access IND. This IND can be submitted for experimental tablets displaying promise in scientific trying out of great and right now lifestyles threatening situation seven as the very last scientific paintings is carried out and the FDA evaluate takes place (21 CFR 312.34).

Criteria for IND utility (14)

- A new indication
- Change in the authorized course of management or dosage level.
- Change in the authorized affected person population (inclined topics e.g. pediatrics, elderly, HIV +ve ,immune compromised)
- Significant exalter ate in the advertising of an authorized Drug.

IND PROCESS IN INDIA (15,16)

FDA's function in the improvement of a new drug starts while the drug's sponsor (commonly the producer or ability marketer) having screened the new molecule for pharmacological pastime and acute toxicity ability in animals, desires to check its diagnostic or healing ability in humans. At that point, the molecule modifications in prison popularity below the Federal Food, Drug, and Cosmetic Act and will become a brand new drug situation to particular necessities of the drug regulatory system.

The IND utility have to comprise facts in 3 wide regions:

- Animal Pharmacology and Toxicology Studies - Preclinical information to allowed evaluation whether the products in reason secure for preliminary checking out in humans. Also blanketedis any preceding revel in with the drug in humans (frequently overseas use).
- Manufacturing Information - Information touching on the composition, producer, stability, and controls used for production the drug substance and the drug product. This fact is classified to make sure that the employer can properly produce and deliver steady batches of the drug.
- Clinical Protocols and Investigator Information - Detail protocols for proposed scientific research to evaluate whether or not the preliminary segment trials will disclose topics to useless risks. Also, data on the qualifications of clinical investigators professionals (normally physicians), who oversee the management of the experimental compound to evaluate whether or not they' recertified to meet their clinical trial duties. Finally, commitments to achieve knowledgeable consent from the studies topics, to achieve assessment of the have a look at via way of m eans of an institutional assessment board (IRB), and stick to the investigational new drug policies.

Once the IND is submitted, the sponsors have to wait 30 calendar days earlier than starting up any scientific trials. During this time, FDA has a possibility to check the IND for protection to guarantee that studies topics will now no longer be subjected to unreasonable risk.

Procedure for new drug approval in India (17)

- The Drug and Cosmetic Act 1940 and Rules 1945 had been passed via way of means of the India's parliament to alter the import, manufacture, distribution and sale of medicine and cosmetics. The Central Drugs Standard Control Organization (CDSCO) and the workplace of its leader, the Drugs Controller General (India) [DCGI] changed into installed. In 1988, the Indian authorities delivered Schedule Y to the Drug and Cosmetics Rules 1945. Schedule Y gives the tips and necessities for scientific trials, which changed into similarly revised in 2005 to deliver it at par with the world over widely wide-spread technique.
- The modification consists of, setting up definitions for Phase I–IV trials and clean obligations for investigators and sponsors. The scientific trials had been similarly divided into categories in 2006. In one class (category A) scientific trials may be performed in different markets with in a position and mature regulatory structures while the ultimate ones fall in to any other class (category B) Other than A.
- Clinical trials of category A (accepted in the U.S., Britain, Switzerland, Australia, Canada, Germany, South Africa, Japan and European Union) are eligible for immediate monitoring in India, and are probable to be acceptedinside8 weeks. The scientific trials of category B are below extra scrutiny, and approve inside16 to 18 weeks.
- A utility to behavior clinical trials in India need to be submitted along a side the data of chemistry, production, manage and animal research to DCGI. The date concerning the trial protocol, investigator's brochures, and knowledgeable consent files need to additionally be attached.
- A copy of the utility have to be submitted to the moral committee and the scientific trials are performed simplest after approval of DCGI and moral committee. To decide the most tolerated dose in humans, destructive reactions, etc. On wholesome human volunteers, Phase I clinical trials are performed. The healing makes use of and powerful dose levels are decided in Phase II trials in 10-12 sufferers at every dose level. The confirmatory trials (Phase III) are performed to generate information concerning the efficacy and protection of the drug in one hundred sufferers (in 3-four centers) to verify efficacy and protection claims. Phase III trials need to be performed on not less than 500 sufferer sun fold throughout 10-15 centers. If the new drug substance isn't always advertised in any other country.
- The new drug registration is carried out after the entirety of clinical trials. The complete facts at the advertising and marketing popularity of the drug in different international locations are likewise required apart from the facts on protection and efficacy. The facts concerning the prescription, samples and checking out protocols, product monograph, labels, and cartons have to additionally be submitted. The utility may be reviewed in quite a number approximately 12-18 months.
- After the NDA approval, while the employer is permitted to distribute and market place the product, it is taken into consideration to be in Phase IV trials, wherein new uses or new populations, long-time period effects, etc. are explored. The drug approval method varies from one country to any other.
- In a few nations, only a single frame regulates the medicine and liable for all regulatory undertaking along with approval of latest tablets, supplying license for production and inspection of producing vegetation e.g. in USA, FDA plays all of the functions. However in a few counties all duties aren't carried out via way of means of a single regulatory authority, along with in India, this obligation is split on Centralized and State government. Other problems in which the distinction seems are, time taken for the approval of a CTA utility, time taken in assessment of advertising and marketing authorization utility, registration fee, registration method and advertising and marketing exclusivity .

NEW DRUG APPLICATION (NDA) (18,19,20)

The New Drug Application is the automobile through which the drug sponsors officially recommend FDA or DCGI to approve a brand new investigational drug on the market and advertising after Phase IIIA Pivot trials.

The professional definition of New Drug is in Sec 201(p) of Federal Drug, Food and Cosmetics Act as;

- Any new drug , the composition of that's such that it isn't always identified amongst specialists certified through medical schooling as secure and powerful to be used below prescribed, advocated or advised situations.
- Any drug the composition of that's such that it due to investigations to decideprotection and efficacy to be used has grow to be identified, however which has now no longer, in any other case in such investigations been used to a cloth extent.

The following letter codes describe the evaluate precedence of the drug;

1. S-Standard evaluate: For tablets just like presently to be had tablets
2. P-Priority evaluate: For tablets that constitute large advances over current treatments.

Classification of medication in NDA

- Center of drug assessment and Research (CDER) classified:
- New drug packagesin step with the kind of drug being submitted and its supposed use:

a. New molecular entity
b. New salt of formerly authorized drug
c. Newsy stem of formerly authorized drug
d. New mixture of or extra tablets
e. Already advertised drug product- Duplication (i.e., new manufacturer)
f. New indication (claim) for already advertised drug (consists of switching advertisingpopularity from prescription to OTC)
g. Already advertised drug product (no preceding authorized NDA) S

PROCESS OF NDA (21,22,23)

The mission of FDA is to put in force legal guidelines enacted via way of means of the U.S. Congress and policies installed via way of means of the Agency to defend the consumer's health, protection, and pocketbook. The Federal Food, Drug, and Cosmetic Act are the basic food and drug regulation of the U.S. With severa amendments, it is the maximum large regulation of its type in the world. The regulation is meant to guarantee purchasers that meals are natural and wholesome, secure to eat, and produced below sanitary conditions; that tablets and gadgets are secure and powerful for his or hermeant makes use of; that cosmetics are secure and crafted from suitable ingredients; and that every one labeling and packaging is truthful, informative, and now no longer deceptive.

Code of Federal Regulations (CFR) (23,24)

The very last policies published in the Federal Register (every day posted file of proposed rules, very last rules, assembly notices, etc.) are accrued within side the CFR. The CFR is split into 50 titles which constitute wide regions situation to Federal policies. The FDA's part of the CFR translates the Federal Food, Drug and Cosmetic Act and associated statutes. Section 21 of the CFR incorporates all policies touching on meals and tablets. The policies report all movements of all drug sponsors which can be required below Federal regulation. 21 CFR Part 314 significance for FDA Acceptance to trade a New Drug, an Antibiotic Drug.

CDER's Manual of Policies and Procedures (MaPPs) (23,25)

These files are accepted commands for inner practices and processes observed via way of means of CDER staff to assist standardize the new drug assessment method and different activities. MaPPs means external activities as well. All MaPPs are to be had for the general public to check to get a higher understanding of workplace policies, definitions, staff obligations and processes.

MaPPS of unique hobby to NDA candidates

- NDAs and BLAs: Filing analysis affairs
- Demanding and Approving Non-Archivable Electronic data for CDER Applications
- Analysis the Same auxiliary Change to More than One NDA or ANDA in More Than One analysis dissection

- Regrets to approve Application for Filing from Applicants in dues
- Activity Packages for NDAs and Efficacy auxiliary.

ABBREVIATED NEW DRUG APPLICATION (ANDA) (26,27,28)

Generic drug packages are cited Abbreviated New Drug Application. Pharmaceutical organizations ought to admit ANDAs and acquire FDA's approval earlier than advertising new time-honored tablets in step with 21CFR 314.105(d).Once ANDA is authorized, an applicant can manufacture and marketplace time-honored drug to offer secure, powerful and occasional value opportunity of innovator drug product to the public. Generic tablets are termed 'abbreviated' as they' renow no longer required to encompass preclinical and scientific information to set up protection and efficacy. They must scientifically display Bioequivalence to Innovator (logo name) drug. A time-honored drug is corresponding to Innovator drug I dosage form, strength, course of management, quality, overall performance and supposed use. One of the approaches to illustrate bioequivalence is to degree the time taken through time-honored drug to attain bloodstream in 24-36 healthful voluanteers. The time and quantity of energeticing redients a with inside the bloodstream ought to be corresponding to the ones of Innovator drug.

Use of bioequivalence as base for approving time-honored drug merchandise changed into hooked up in 1984, additionally called WAXMAN-HATCH ACT. It is due to this act that time-honored tablets are inexpensive with out accomplishing expensive and duplicative clinical trials.

PROCESS OF ANDA (29,30,31)

The Federal Food, Drug, and Cosmetic Act are the fundamental meals and drug regulation of the United States. The regulation is meant to guarantee purchasers that foods are natural and wholesome, secure to eat, and produced below sanitary conditions; that tablets and gadgets are secure and powerful for his or hermeant makes use of; that cosmetics are secure and crafted from suitable ingredients; and that every one labeling and packaging is truthful, informative, and now no longer deceptive.

The Code of Federal Regulations report maximum movements of all drugs candidates can be required below Federal regulation. The following policies immediately practice to the ANDA method:

- 21CFR Part 314: significance for FDA Acceptance to trade a New Drug
- 21CFR Part 320: Bioavailability and Bioequivalence necessary.

INVESTIGATION OF MEDICINAL PRODUCTS DOSSIER (IMPD) (32,33,34)

The IMPD is the idea for approval of scientific trials through the capable in the EU. The Clinical Trial Directive got here in pressure harmonizing the laws, guidelines and administrative provisions of the Member states regarding the implementation of GCP within side the behavior of clinical trials on therapeutics for human use. The directive delivered a harmonized process for the authorization to carry out a scientific have a look at in any person of the EU Member States. In addition, it defines the documentation to the documentation to be submitted to the Ethics Committee in addition to the IMPD to be submitted to the capable authority for approval.

Dossier: A series of files approximately a selected individual, occasion or situation. E.g. Patient's clinical record.

Medicinal product dossier: File containing particular statistics approximately a selected drug product.

Objectives: (35)

Since clinical trials will regularly be designed as multi middle research, doubtlessly concerning distinct Member States, it's miles the purpose of this tenet to outline harmonized necessities of the documentation to be submitted in the course of the European Country.

INVESTIGATOR'S BROCHURE (36,37,38)

The Investigator's Brochure is a collection of the scientific and nonscientific data at the analytical product(s) which might be relevant to the have a look at of the product(s) in human topics.

Purpose: (39)

- Its motive is to offer Information to the Investigators and others worried within side the trial together with the dose, dose frequency/interval, techniques of management, and protection tracking process.
- The IB additionally presents perception to help the scientific control of the have a look at situation throughout the route of the clinical trial.
- The record sought to be supplied in a concise and easy manner.
- IB allows a clinician or capability investigator, to apprehend it and make his/her personal independent chance gain evaluation of the appropriateness of the proposed trial. For this reason, a medically certified individual ought to usually take part within side the modifying of an IB.

GENERAL CONSIDERATIONS: (40,41)

Title Page

1. Sponsor name
2. The identification of every investigational product (i.e., studies number, chemical or authorized time-honored name, and exchange name(s) in which legally permissible and favored through the sponsor).
3. The release date.
4. Confidential declaration

Confidentiality Statement

The sponsor might also additionally desire to encompass a declaration educating the investigator/recipients to deal with the IB as a personal report for the only records and use of the investigator's crew and the IRB/IEC.

The investigator brochure ought to encompass:

1. Table of Contents
2. Summary
3. Introduction
4. Description of IB
5. Nonclinical Studies
6. Effects in Humans
7. Abstract of Data and instruction for the Investigator.

CONCLUSION

In this review, we highlighted the maximum current and applicable elements vital to behavior non-clinical research to wait the suggestions to broaden new pills recommended with the aid of using fore most regulatory agencies. Although notable efforts in current years had been going on to reduce, and possibly in the future, ban the usage of animals in the method of recent drug improvement, numerous opportunity techniques are being followed and endorsed with the aid of using the primary worldwide regulatory agencies. However, the usage of animals in the new drug improvement method remains required. The use of GLP requirements is truly vital, specially for the assessment of protection research, and is a decisive component for the attractiveness of non-scientific research in different international locations in which GLP has been endorsed on account. Although in some country adopts almost the equal procedures (suggestions) endorsed with the aid of using the FDA and EMA, few laboratories or country wide establishments can behavior non-scientific research according with GLP necessities vital for brand spanking new drug registration purposes. The loss of reproducibility and reliability of non-scientific research has been a proscribing component in the method of recent pills improvement for a few country wide pharmaceutical

companies. Therefore, the need for excessive pleasant fashionable animals, related to well-designed protocols, certified human resources, use of nice and bad controls, blind test execution, right use of statistical analyses, amongst different elements, are obligatory elements to gain dependable and reproducible non-scientific results. Non-clinical research have to be strictly accomplished according with appropriate institutional medical practices and additionally using GLP necessities (quintessential for the request and approval of a IND) in an effort to make certain the pleasant, reproducibility and reliability of non-clinical data, in an effort to help the early clinical research contributing to the a success improvement of a new drug.

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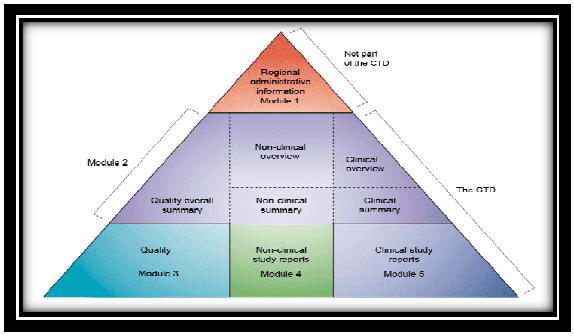

Fig.1.Non-clinical development in CTD modules

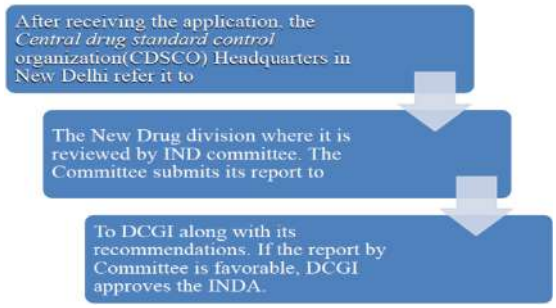

Fig.2.Procedurefor new drug approval in India

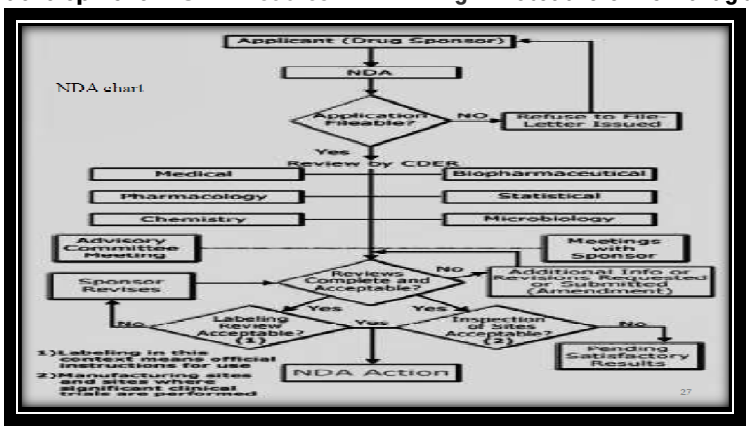

Fig.3.CDER's Manual of Policies and Procedures (MaPPs)

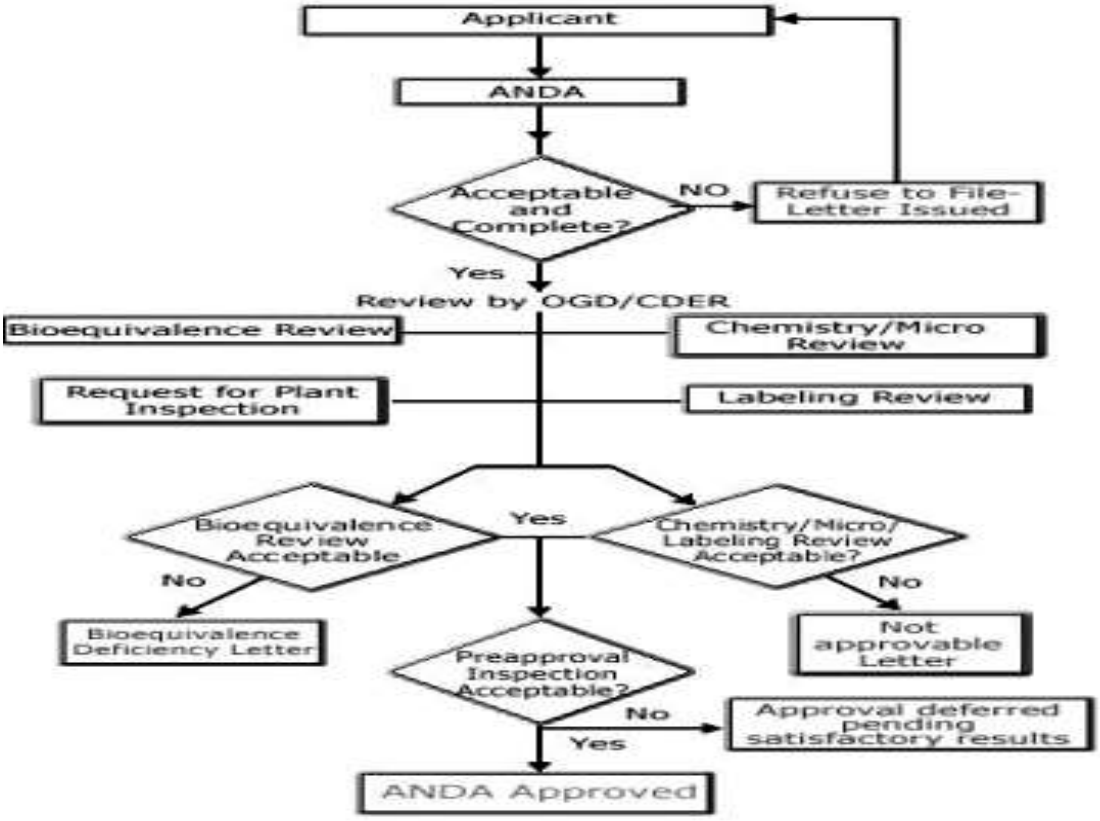

Fig.4.PROCESS OF ANDA

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RESEARCH ARTICLE

Baclofen in Treatment of Neuropathic Pain

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ABSTRACT

Baclofen is a centrally acting skeletal muscle relaxant pharmacologically and BCS class III pharmaceutically. It is FDA approved drug used in the treatment of muscle spasticity, localized neuropathic pain, management for the relief of flexor spasms, clonus and concomitant pain, common sequelae of spinal cord lesions and multiple sclerosis. Baclofen also has several off label uses. Baclofen (beta-[4-chlorophenyl]-GABA) is an agonist of gamma-aminobutyric acid at beta subunit and has action on mono and polysynaptic neurons at the spinal cord level and brain. Currently baclofen is available for oral, transdermal and intrathecal administration through pump infusion.

Keywords: Baclofen, Neuropathic pain, Mechanism of action

INTRODUCTION

Neuropathic pain is a common problem in clinical practice [2]. Neuropathic pain may be resistant to usual doses of analgesic medications. Neuropathic pain may be considered to be pathophysiologic because it arises from peripheral or central nervous system injury and serves no obvious protective function [3]. Neuropathic pain, a challenging pain category which is considered to be particularly difficult to treat. Diabetes, immune deficiencies, malignant diseases, traumatic and ischemic disorders seems to rise neuropathic pain [4]. Neuropathic pain generally presents with a combination of painful and non painful symptoms, including : spontaneous ongoing (notably burning) pain, paroxysmal pain, allodynia, hyperalgesia, after sensation, summation of pain, paresthesias, dysesthesias, and sensory deficit in the painful area [5].

Baclofen is a centrally acting skeletal muscle relaxant used in the treatment of spasticity, management of pain, treatment of various neuropathic pain such as diabetic neuropathic pain, peripheral neuropathic pain, localized neuropathic pain. Apart from these, it is used in the treatment of alcohol use disorder. Baclofen is a racemic mixture , it comprises of equal amounts of R- and S- enantiomers. Racemic baclofen is often given orally with a reported bioavailability of 70-80% clinically [6]. Baclofen shows saturable absorption because the bioavilability of baclofen has been reported to decrease with increasing doses [7]. Baclofen is found to be a prototypical $GABA_B$ receptor agonist. Baclofen is the only $GABA_B$ receptor agent approved for clinical use [7]. Among racemic baclofen, R9(-) enantiomer reside $GABA_B$ agonistic activity primarily[8]. Racemic baclofen (R,S- baclofen) is an optically active compound [8]. It is found that R-isomer is more effective action than the racemate. There is a clear stereo selectivity at the $GABA_B$ receptor site for R-baclofen [6]. It has been identified that there is a presence of binding site of positive allosteric modulation of GABAB receptors topographically distinct from that of neurotransmitter GABA[7].
This article is aimed to review the role of baclofen in the management of neuropathic pain.

NEUROPATHIC PAIN

Neuropathic pain [NP] is caused by a lesion or disease of the somatosensory system, including peripheral fibres (Aβ, Aδ, C fibres) and central neurons [9]. Clinically, neuropathic pain is characterized by spontaneous ongoing or shooting pain and evoked amplified pain responses after noxious or non-noxious stimuli [10]. The International Association for the Study of Pain (IASP) defines NP as "pains resulting from disease or damage of the peripheral or central nervous system, and from dysfunction of the nervous system"[11]. NP will negatively impacts the quality of life and aggravates functional decline [12]. The notable features of neuropathic pain processes are widespread pain not otherwise explainable, evidence of sensory deficit, burning pain[13]. The features that differentiate NP from other types of pain include the pain and sensory symptoms that persist beyond the healing period [14].

BACLOFEN

Baclofen belongs to the class of skeletal muscle relaxants [15].Chemically , baclofen is ϒ-amino-β-[p chlorophenyl]-butyric acid derived from the inhibitory neurotransmitter ϒ-aminobutyric acid (GABA). Patients with multiple sclerosis or with spinal or cerebral disorders, muscle spasticity can be treated with baclofen [16]. Baclofen is a centrally acting skeletal muscle relaxant [16]. It has many other medical uses besides treatment for spasticity. Baclofen is effective in treating alcohol dependence, lower back pain, gastroesophageal reflux disorder (GERD), epilepsy, depression disorder [17,18,19,20] etc.

Pharmacodynamics

$GABA_B$ receptors are major inhibitory neurotransmitter found throughout neuroaxis and in some peripheral tissues[19]. Baclofen is a prototypical $GABA_B$ receptor agonist has an affinity for the receptor similar to GABA. Administration of baclofen produces analgesia in acute and chronic pain models. This response is due to the $GABA_B$ receptor mediated inhibition of substance P and from primary afferent terminals. The inhibition of subastance P release modifies neurokinin-1 receptor levels in the dorsal horn and thereby decreasing the transmission of pain impulses [21, 22]. The R(-) baclofen is reported having skeletal muscle relaxant property [21]. $GABA_B$ receptors are present and functional active in schwann cell of peripheral nervous system. Except for the CNS, $GABA_B$ receptors are found in cutaneous layer on C fibres and keratinocytes. Therefore these receptors provide a new target for the topical treatment of localized neuropathic pain. Topical baclofen was shown to be effective in pain relief [21,23,24].

Mechanism of Action

The precise mechanism of action of baclofen is not fully understood yet. Baclofen inhibits both monosynaptic and polysynaptic reflexes at spinal level and decreases the excitatory neurotransmitter release from efferent terminals [25]. Since baclofen is a structural analog of inhibitory neurotransmitter GABA and may exert its effect by stimulation of $GABA_B$ receptor subtype [26]. Topically site of action of baclofen is C fibres [25].

Case reports and pilot studies

Jon-Paul Harmer et al conducted a case study in a 64 year old female patient who had chief complaint of back pain, bilateral leg pain, and generalized myalgia. She had been diagnosed with polymyositis and scleroderma and diagnosis was preceded by severe generalized muscle pain. MRI scan showed severe degenerative spine changes, dorsal kyphosis and other rotational changes, and anterolisthesis of L3 body. She also had spinal stenosis with multiple bulging disks, worse at the L3-4 level. At the time she was seen in their clinic, reported her worst pain in her right buttocks extending into the right leg and foot. She also described generalized pain throughout her body especially the lower and upper extremities that she characterized as aching, burning, and throbbing. Initially her medications included controlled release morphine 60 mg tablets, she reported taking 15 tablets every 6 hours for a total of 3,600 mg of morphine daily. In addition, she was taking prednisone 7.5 mg daily, gabapentin 100 mg twice daily, zolpidem 30 mg at bedtime, diazepam 10 mg four times daily, promethazine 50 mg as needed for nausea, celecoxib 200 mg twice daily, methocarbamol 750 mg every 4 hours as needed, glucosamine and chondroitin one tablet three times daily, and acetaminophen as needed. Relevant medical findings of her case included neuropathic pain and spasticity (grade 1) in her right thigh, degenerative changes in her cervical spine, lumbar spinal stenosis, polymyositis and scleroderma primarily affecting the upper and lower extremities, and anxiety not otherwise specified. In 2001 an intrathecal pump was implanted surgically to her. Prior to the placement of intrathecal pump she had reported pain (score9/10)and she reported moderate relief after a trial of intrathecal opioid and low dose bupivicaine (pain score 6/10). However, after addition of a 50 mcg intrathecal baclofen bolus dose, her pain was 2/10 within 6 hours after the bolus for the first time. After this successful trial of pain reduction, the pump was filled with hydromorphone 50 mg/mL, bupivacaine 25 mg/mL, and baclofen 500 mcg/mL with a final volume of 11 ml. At 1 month follow-up visit , patient's pain was still well controlled with a pain intensity rating of (pain score4/10) for her right hip and leg, and 0 for the rest of her body. Six months later she continues to rates her pain as (score4/10) and states she is 80% better than she was prior to pump placement. From this clinical study they concluded that the remarkable response of this patient to intrathecal baclofen indicates that further study is warranted into the analgesic effects of intrathecal baclofen for chronic pain that has not responded adequately to traditional analgesics[30].

Hatice Kumru et al conducted a research study to highlight that intrathecal baclofen (ITB) bolus has significant analgesic effects in neuropathic pain. Spinal Cord Injury patients with a cervical or thoracic lesion and neuropathic pain were randomized to receive either a single ITB bolus or placebo. Patients were randomly assigned to two groups, 1) ITB bolus group and 2) placebo group. Randomization was based on computer –generated randomization list. ITB bolus group: A baclofen bolus of 50µg was injected intrathecally at the L3/L4 level. If this did not alleviate pain effectively, they injected a 100µg bolus, at least one week later based on the dose dependent antinociceptive effect produced by baclofen in animals. They used 50µg of ITB, as this is the standard test dose in patients with SCI-associated spasticity, established to be both effective and safe. Furthermore, a 50µg ITB bolus increased pain perception threshold and reduced acute pain perception in patients with SCI. Placebo group was injected with 1 ml of physiologic sodium chloride subcutaneously at the L3/L4 level at the same location where ITB was otherwise injected. Subcutaneous placebo injections were preferred to intrathecal injections in order to avoid complications. Improvement in overall pain evaluation and continuous pain was evident during 24 hours was noticed in the clinical study. In conclusion, their results document clear analgesic effects of a single ITB bolus on all subtypes of neuropathic pain. The beneficial effects of baclofen achieved with minimal side effects and with good tolerability by administiringintrathecally. Therefore this study opens discussion about the possible application of ITB for neuropathic pain control [31].

Kuldeep Nigam et al developed a poly (d,l-lactide-co-glycolic acid) (PLGA) nanoparticles of baclofen were developed for neuropathic pain management and optimized using nanoprecipitation method. They developed baclofen loaded PLGA nanoparticles of average particle size 124.8 nm, polydispersity index of 0.225, and zeta potential was found to be in the range of -20.4 mV. In vitro dissolution studies showed that baclofen was released from PLGA nanoparticles in a sustained manner from 50% release in 2.5 hours to 80%–85% in 24 hours. The intra nasal route was chosen by the researcher to explore the nose to brain drug uptake pathway for neuropathic pain[32].

In vivo studies of the research involving gamma scintigraphy showed prolonged retention of the nanoparticles in brain unlike aqueous drugs, which were confirmed by biodistribution studies suggesting PLGA as suitable carrier of baclofen in the form of nanoparticles for combating neuropathic pain conditions. Goran Lind et al conducted a long term pilot study using patients for 67 months and the study demonstrates that a deficient spinal cord stimulation(SCS) effect in neuropathic pain may be considerably improved by intrathecal baclofen administration, and that this enhanced effect persists for a long-time. In the previous study they addressed the possibility to increase the effectiveness of spinal cord stimulation (SCS) applied for neuropathic pain by using adjunct pharmacological therapy. This study demonstrates that in the long-time perspective the combined treatment with SCS and intrathecal baclofen may prove effective for selected patients [33]. Intrathecal administration of baclofen shown to be effective in the relief of pain as well as spasm-related pain and pinch-induced pain. In a double-blind randomised control study, baclofen decreased dysesthetic pain (continual spontaneous burning, lancinating, shooting, radiating knife-like feelings) [34]. Valerio magnaghi et al conducted a research study to test if neuropathic pain is related to nerve degeneration, whether the modulation of peripheral GABAB receptors may promote nerve regeneration and decrease neuropathic pain. They used partial sciatic ligation –(PSL) induced neuropathic model. Simultaneous 7 days co administration of baclofen (10mg/kg) and CGP56433(3mg/kg) alters tactile hypersensitivity. They concluded that peripheral synergestic effects, through $GABA_B$ receptor activation, promote nerve regeneration and likely relief neuropathin pain[35].

Terezinha de jesus t. Santos et al conducted experiment to study the effect of baclofen in experimental neuropathic pain. Thirty-three male Wistar rats, weighing 250-300g, were used for the experiment. Baclofen in doses of 1, 2, 4 and 8 mg/kg, peros, was used. Behavioural observations and thermal tests were done after 2 hour administration of baclofen. The behavioural analysis of the experimental rats showed a significant increase of the scratching behaviour from the 2nd post-operative day up to four months, defining the chronic condition. They concluded that the study has shown that scratching behaviour, as a spontaneous expression of chronic experimental neuropathic pain, is depressed by baclofen in a dose-dependent fashion [37]. David J. Kopsky et al conducted a case study with a 74 year old woman with a partial spinal cord injury lesion at L4 complained of tingling, pins and needles, and burning in her legs. She was treated with pain medication tablets pregabalin 450 mg, acetaminophen 3000 mg, and diclofenac 150 mg daily at the time of first consultation. She scored the pain intensity by 6 on the 11 point numerical rating scale. She was also suffered with reduced stability and balance due to hip extensor weakness. Then the treatment was added with baclofen 5% cream. The cream was applied for 2 to 3 times daily on the neuropathic areas as an analgesic provided additional pain reduction. After one month treatment, the patient reported that the tingling, pins and needles, and burning were completely vanished after application of the baclofen cream, without experiencing any side effects such as dizziness, drowsiness, and muscle weakness seen in oral baclofen treatment. This case points pivotal aspect that baclofen 5% cream is able to control neuropathic pain in a case with paraplegia [38].

CONCLUSION

The case study reports and pilot study reports demonstrates that the drug baclofen is effective in the treatment of both chronic and acute neuropathicpain compared with other analgesics and NSAIDs. Therefore, baclofen can be considered as the drug of choice for physicians in the management of neuropathic pain.

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RESEARCH ARTICLE

In-vitro Antimicrobial Efficacy of SNP Synthesized from *Aloe vera* (Barbadensis) and Screening of its Phytochemicals Accompanied by Structural Characterization.

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ABSTRACT

Silver nanoparticles(SNP) have exclusive properties which are used in molecular diagnostics, therapies and numerous medicinal trials. Silver nanoparticles (SNP) produced by chemical sources, has hitches with toxicity and stability. To overcome this, the natural or green method offers a feasible substitute. The microwave accelerated silver nano-particles were synthesized by using Aloe Vera extract (gel) and have been assessed for its antimicrobial efficacy, stability and toxicity. The synthesized nanoparticles were found to be fungicidal along with bactericidal and had maximum anti-microbial activity at 100µl concentration of plant extract. The antimicrobial efficacies were checked against *Staphylococcus aureus, Bacillus cereus* as gram positive bacteria and *Pseudomonas aeruginosa and Klebsiella pneumonia* as gram negative bacteria. For evaluation of antifungal activity, *Aspergillus niger* and *Candida albicans* were checked. After incubation at 37 °C for 24 hrs, different levels of zone of inhibition were measured. The determinations were done in triplicate and the mean values ± SD were presented. The diameters of bacterial inhibition zones (mm) measured for *Staphylococcus aureus* was 19.33± 0.57 mm and *Bacillus cereus* was 15.3± 0.57 mm whereas, for Gram negative bacteria, *Klebsiella pneumonia* was 13.66 ±1.52 *mm and Pseudomonas aeruginosa* was 18.6 ±0.52mm.Against fungi*, Aspergillus niger and Candida albicans,* the inhibition zones measured were 6.6± 0.57 and 14.6± 0.56 mm respectively. Silver and Aloe Vera have been widely used as an antimicrobial agent for centuries; the recent development in interest due to increasing danger of antibiotic resistant microorganisms, caused by excessive use of antibiotics. So, in the search of inexpensive and effective pathways; researchers used Aloe Vera extracts (phytochemicals) for

synthesizing new effective drugs which have high medicinal values as well as being environmentally friendly.

Keywords: Silver nanoparticles, *Aloe Vera*, antimicrobial agent, green-synthesis, Aloe-nano-silver, Phytochemicals

INTRODUCTION

As it is well known that nanotech is one of the most energetic zones of research for modern material sciences [1,2]. From the ancient time silver has been documented for its strong antimicrobial efficacy against a wide range of micro-organisms including bacteria and fungi both. Silver has been explored as disinfectant; for treatment of wounds and burns because of its broad-spectrum noxiousness to bacteria [3,4,5] Many researchers have explored about the various properties such as catalysts, optical, electrical and antimicrobial of Silver nanoparticles (SNP). Numerous approaches for synthesis of silver nanoparticles are available, but, an emergent necessity to develop an eco-friendly route without consuming toxic chemicals is gaining importance [5,6,7]. However, the green synthesis by use of plants for the production of nanoparticles has drawn attention and it's a rapid, economical, eco-friendly too.[8,9] Plant based biosynthetic procedures have arose as a viable substitute to chemical and physical procedures [4,10,11,12,16]. Green synthesis of SNP has aids to the reduction and steadiness of metal ions due to presence of various biomolecules in plants as metabolites owning bio-stabilization and bio-reduction ability, and because of this study of such molecules could aid to controlled size and morphology of nanoparticles [13,14,15,16].

Plant extracts may perform both as stabilizing and reducing agents in the production of metal-based nanoparticles due to their (plant extract) well known composition which influences the properties of the nanoparticles [16,17,18,19,20,21]. This is because different extracts comprise different concentrations and combinations of organic reducing agents [20]. Usually, a plant extract-mediated bio-reduction includes mixing the aqueous extract with an aqueous solution of the pertinent metal salt. As numerous diverse chemicals are involved, the bio-reduction process is comparatively complex [20]. Many researches stated that the water-soluble heterocyclic and polyol components are generally accountable for the stabilization and reduction of silver ions respectively. Furthermore, it was stated that phytochelatins/ Phytochelatin synthase, C-S lyase, oxidoreductase/ quinines, heparins, Chitosan, NADH dependent reductase; Amino, carboxyls, thiol moieties, β-d-glucose; present in plant as metabolites; terpenoids and polyphenols such as flavanols, flavonoids, and isoflavones and anthocyanins of plants are responsible for biogenesis of nanoparticles, examples are enlisted[8,54] in *Table 1.3.*The Biological methods of synthesizing SNP have surfaced a way for the "greener synthesis" and also have been confirmed to be better source due to controlled synthesis, sluggish kinetics, and stabilization [22,23,24,52].

This research article is mainly stating about the 'ecofriendly, rapid and more stable' method for the synthesizing SNPs by using *Aloe Vera* and also probable mechanism of phytochemical constituents present in its leaf extract, along with evaluation of its antimicrobial efficacy. This is a simple, effective, low cost and eco-friendly process for synthesizing silver nanoparticles [25,26,27,28]. Aloes are the large genus of plants containing over 500 species belonging to *Asphodeloideae* family widely distributed in China, Japan, Russia, South Africa, the United States, Jamaica, Latin America, India, sub-Saharan Africa, Madagascar and parts of Arabia. *Aloe Vera* is acknowledged to have seventy-five nutrients that are twenty minerals, twenty amino acids, twelve vitamins and water. *Aloe Vera also* have several bio-chemicals such as, alkaloids, steroidal lactones, tannin and flavonoids, which have key role in shape-directed formation of SNPs [26,29,30,60]. Many researchers revealed about the medically important properties *Aloe*, for instance, as antiviral, as acaricidal which shows activity against skin infections (such as herpes, acne, and scabies), anti-inflammatory, analgesic, wound healing, immunity booster and anti-tumor, as antiviral, anti-bacterial, and antifungal properties [31,32,33,34,35]. *Aloe plants* are shrubby, succulent, perennial, pea green in color. In This study *Aloe* species, which was used for synthesis of SNP was *Aloe Vera* (*Linn*), also known as *Aloe Vera (Barbadensis)*,

which belongs to the family of *Liliaceae* and is generally distributed in Africa, Asia, and other tropical areas. It is a succulent stemless plant growing up to 60-100 cm tall with thick and fleshy green leaves along with white flecks on the upper and lower stem surfaces; margin of the leaf is serrated and has small white teeth [26,36,37]. shown in *figure 1.1.* It is a stemless or very short-stemmed plant spread by offsets and root sprouts growing to 80-100 cm tall in length.

It also comprises some active compounds such as Aloesin, Aloin, Aloe-emodin, Aloemannan, Acemannan, Aloeride, Naphthoquinones, Methyl Chromones, Flavonoids, Saponin, Sterols, Amino acids and Vitamins. The levels of these compounds are highly variable according to species and strain, as well as growth conditions in *Aloe Vera* plants. [36,38,39] Leaf consists of inner gel and outer rind. The chemical composition of leaf pulp includes anthraquinones, anthrones, chromones, carbohydrates, enzymes, essential and non- essential amino acids, lipids, inorganic compounds, vitamins, proteins, and miscellaneous organic compounds. [4,19,34,37,40] In SNP synthesis *Aloe-Vera* acts as both reducing and stabilizing mediators. This is an alternative method for the production of Silver nanoparticles by plant extracts and has arisen as a simple and viable substitute to chemical and physical procedures.[64]Synthesis of quasi spherical silver nanoparticles using a purified apian compound, extracted from *Aloe* leaf gel was used to produce silver nanostructure at ambient conditions. The aqueous based *Aloe* gel was used to produce silver nanostructure at ambient conditions for the silver nanoparticles synthesis. [41,42]The antibacterial activity against various human pathogenic gram positive and Gram-negative bacteria such as *Staphylococcus aureus, Bacillus cereus, Pseudomonas aeruginosa, Klebsiella pneumonia, Escherichia coli* respectively and Fungus such as *Aspergillus niger* and *Candida albican* was undertaken.

MATERIAL AND METHODS

Materials and Chemicals

0.01M $AgNO_3$ stock solution,0.001M $AgNO_3$ working solution, *Aloe* Vera extract (prepared), distiller water, Whatman no.1 filter paper, magnetic stirrer, conical flask and beaker.

Preparation of Plant Extract

Fresh leaves of *Aloe Vera* were collected, were thoroughly washed by using sterile distilled water, and cut into 1.0 inches size. The gel was extracted from the leaves by using a clean spoon. 25 g of extracted gel was finely chopped into small pieces and was grinded by using mortar and pestle. After grinding, the gel was mixed with deionized water in equal volume (1:1) and heated for 5 minutes in the microwave at 300 W. Then the solution (extract) was cooled and was kept at 4°C in the refrigerator overnight. Then the solution (extract) was filtered through Whatman's filter paper.

Preparation of metal solution

5mM Silver Nitrate solution (Merck India Ltd), weighed 0.084 g was dissolved in 100 ml distilled water.

Synthesis of silver nanoparticles

50 ml of *Aloe Vera* plant gel extract was mixed with 50 ml of 5mM aqueous sol. of silver nitrate in 1:1 proportion and kept at room temperature for 48 hours at shaker for the development of reddish brown colour. To attain much smaller particles, solution was centrifuged at 10,000 rpm for 10 minutes and then examined the supernatant for the synthesized particles, [13,43] shown in *figure 1.2.*

Evaluation of antimicrobial efficacy

Preliminary analysis of antimicrobial activity was conducted by using Agar well diffusion assay. The antimicrobial abilities were tested against *Staphylococcus aureus*, *Bacillus cereus* as Gram positive bacteria and *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Escherichia coli* as gram negative bacteria. Bacterial samples inoculum was prepared in peptone broth and incubated for 4 hours. Then 0.1 ml of inoculum was homogeneously inoculated and

spread by sterile glass spreader on Petri plates containing MH Agar (Himedia Laboratories) medium. The wells of 6mm diameter were punctured on it by using sterile cork-borer and 50 µl of *Aloe Vera* based synthesized Silver Nanoparticles were poured into the wells using sterilized micropipettes. The determinations were done in triplicate and all plates were incubated for 24 hrs. at 37 °C, aerobically. *Aloe Vera* gel extract was used as negative control. The diameters of inhibition zones were determined in mm. For fungal samples, inoculum was prepared in SDB solution and incubated for 4 hrs. Then 0.1 ml of inoculum was homogeneously inoculated on petri plates containing SDA medium, then wells of 6 mm diameter were punctured on it by using sterile cork-borer. A 50 µl of biologically synthesized Ag-NPs was loaded in the wells using sterilized micropipettes. Sterile SDB water was used as a negative control. Plates were incubated for 24-48 hrs. at 27 °C. Zone of Inhibition in mm was determined. [1,7, 44,45,46,64]

Characterization of SNPs

Following methods were used for the characterization of Aloe based SNPs:

UV–vis spectroscopy

The reduced pure Ag^+ ions was observed at 300- 430 ηm. Spectrum of the reaction was carried out by diluting a small aliquot of 100 µl of the sample into 1.0 ml DH_2O. [47,48,49]

Transmission Electron Microscopic (TEM)

Thin film of the *Aloe* based SNP solution was prepared on carbon coated copper grid by adding a drop of the sample on it, and then the film was allowed to be dried under mercury lamp for 5 minutes. Then images were observed on screen [27,28,47].

XRD (X-ray diffraction)

X-ray diffraction was mainly carried out to confirm the crystalline nature of the silver nanoparticles. [47] Powder XRD patterns were examined using a powder X-ray diffractometer. The sample was dried at 40 ^{0}C in the incubator and then the sample was run at X-ray diffractometer. The mean particle size (dia) of SNP was calculated through the XRD pattern, according to the line width of the plane, refraction peak, using the following Scherrer equation: $D = K\lambda / \beta 1/2 \cos \theta$**.** In this the reference peak width is at angle θ, where λ denoted for X-ray wavelength, $\beta 1/2$ represents the width of XRD peak at half height and K shows the shape factor.

FTIR

FT-IR analysis was thru diffuse reflectance mode run at resolution of 4 cm-1 in the range of 400 to 4,000 cm-1 for the evaluation of functional groups involved in the synthesis of silver nanoparticles. The extract was dropped on a FTIR disc (Real Crystal IR Card, 9.5 mm aperture). Then the cards were inserted into the Nicolet FTIR spectroscopy. Scanned samples passed through an infrared beam, with the detector connected to a computer displaying the sample spectrum, later the absorbance plot was formed against the wave number.

Screening of Phytochemicals

Qualitative Analysis

Test for Alkaloids: About 0.5 ml of extract was added in 5 ml of 1% HCL and kept in a boiling water bath. 1 ml of filtrate was mixed with a few drops of Meyer's reagent. If turbidity or the precipitate observed, was taken as an indicator for the presence of alkaloid [9,46].

Test for Tannins: About 0.5 ml of *Aloe* extract was mixed with 10 ml boiling deionized water and filtered. A few ml of 6% $FeCl_3$ was added to the filtrate, and the appearance of a deep green colour confirmed the presence of tannins [9,46].

Test for Flavonoids: About 0.2 ml of the extract was dissolved in CH_3OH and heated, and a pinch of Mg metal added to the mixture, followed by a few drops of HCl. The appearance of a reddish orange colour indicated the presence of flavonoids [9,46].

Test for Phenolic Compounds: About 0.5ml of *Aloe* extract was dissolved in 5 ml deionized water. Then 2-3 drops of neutral 5% ferric chloride solution were added into it. Appearance of dark green colour indicates the presence of phenolic compounds [9,46].

Test for Reducing Sugars (Fehling's Test): The aqueous-ethanol *Aloe* extract (0.5 ml of plant extract in 5 ml of distilled water) was added to boiling Fehling's solution (A and B), and appearance of yellow or brownish red indicated the presence of reducing sugars [9,46].

Test for Saponins: About 0.5ml of *Aloe* extract was added 5 ml of deionized water in a test tube. The solution was shaken vigorously and observed for a stable persistent froth. The froth solution was mixed with 3 drops of olive oil and shaken vigorously after which it was observed for the formulation of emulsion [9,46].

Test for Terpenoids (Salkowski Test): 0.5 ml of *Aloe* extract was added into 2 ml of chloroform solution. Then 3 ml of conc. H_2SO_4 was carefully added into it to form a layer. A reddish-brown color interface indicates the presence of terpenoids [9,46].

Quantitative Analysis

Determination of Alkaloids: About 5g of *Aloe* gel extract was added in 200 ml of 10% acetic acid, then covered and kept for 4 hours. After that the solution was filtered and concentrated up to one-quarter of the original volume, at a water bath. Then concentrated ammonium hydroxide was added drop wise till the precipitation part was completed. Then the whole solution was allowed to settle. After this procedure precipitates were collected and washed with dilute ammonium hydroxide and filtered. The residue was confirmed as alkaloid, which was then dried and weighed.

Estimation of Flavonoids: About 1 ml of plant extract in methanol (10mg/ml) was mixed with 100µl of 20% Aluminium Trichloride in methanol and a drop of acetic acid, and then diluted with methanol with 5 ml. Incubated at 25°C for 40 minutes. Absorption was measured at 415 nm at UV/Visible spectrophotometer. For Blank 100ml of plant extracts and a drop of Acetic acid, diluted with 5 ml methanol was prepared. For a set of reference standard solutions, quercetin (0.5mg/ml) in methanol at 20, 40, 60, 80 and 100 µg/ml were prepared.

Estimation of Total Phenolic Compounds: About 100 mg of the *Aloe* extract was dissolved in 100 ml of Triple distilled water (TDW). 1 ml of this solution was transferred to a test tube. Then 0.5 ml 2N F-C reagent along with 1.5 ml 20% of Na_2CO_3 sol were added to it. Then the total vol. was made up to 8.0 ml with TDW and allowed vigorous shaking. After that it was kept standing for 2 hours. Then absorbance was measured at 765 nm. Standard curve was prepared with different concentrations of Gallic acid (20, 40, 40, 60, 80 and 100 µg/ml).

Determination of Total Saponins: About 20g of *Aloe* extract was mixed with 200 ml of 20% aqueous ethanol. This sol was heated at 55°C (in water-bath) for 4 hrs. Then the mixture was filtered and residues were re-extracted in the next 200 ml of 20% ethanol. Both extracts were collectively reduced to 40 ml (at 90 °C in a water bath). Then this concentrated solution was shifted to Separating funnel (250 ml) and then 20 ml of diethyl ether sol. was added to it (shaken vigorously). Then the aqueous layer was collected and discarded. The purification process was repeated with 60 ml of n-butanol. The combined n-butanol extracts were eroded two folds with 5% aqueous sodium chloride

(10 ml) and leftover sol was heated (by using water bath). After the evaporation process the sample was dehydrated in the hot air oven to a constant weight; then the amount of Saponin content was measured.

Estimation of Tannins: 0.1 ml of the *Aloe* extract was added in 7.5 ml of distilled water, then 0.5 ml of Folin-Ciocalteu phenol reagent was added along with 1 ml of 35 % Na_2CO_3 solution and then dilute it with 10 ml distilled water. The mixture was shaken well and kept at 25°C for 30 min. The standard graph, solutions of Gallic acid 20, 40, 60, 80 and 100 µg/ml were prepared. Absorbance was measured against the blank at 725 nm.

Determination of Terpenoids: About 100g of *Aloe* extract was taken and soaked in ethanol for 24 hrs. The extract was filtered and filtrate was extracted with petroleum ether. The ether extract was treated as total terpenoids.

RESULTS AND DISCUSSION

Synthesis of Silver nanoparticles

Aloe Vera and Silver nanoparticles both are very much known for their antimicrobial actions. When *Aloe* and silver are unified together, their efficiency to cause antimicrobial efficacy increases and can be an excellent substitution for the development of novel antibacterial agents. For the biosynthesis of silver nanoparticles by *Aloe Vera* (*Barbadensis)* were used to reduce silver ions into silver nanoparticles. When 50 ml of *Aloe Vera* plant gel extract was mixed with 50 ml of 5mM aqueous $AgNO_3$ sol in 1:1 proportion and incubated at room temperature for 24- 48 hrs., it develops of red-brown colour which clearly indicated the synthesis of SNPs which was further reconfirmed with UV–vis spectrophotometer examination (*Figure 1.2).*

Antimicrobial efficacy

It was evaluated against pathogenic microbes comprising bacterial strains as well as fungi by using Agar well diffusion assay. After incubation at 25 °C and 37°C for 24-48 hours for fungi and bacterial strains respectively, different inhibitory zones were measured. Water based *Aloe Vera* gel served as negative control for these assays (*Table 1.9*). The determinations were done in triplicate and the mean values ± SD were represented in graphical form and shown in *Graph 1.8.* The diameters of bacterial inhibition zones (mm) measured for Gram positive bacteria, *Staphylococcus aureus* was 19.33± 0.57 mm (*figure: 1.6*)and *Bacillus cereus* was 15.3± 0.57 mm (*figure:1.6*) whereas for Gram negative bacteria, *Klebsiella pneumonia* was 13.66 ±1.52 mm (*figure: 1.6)*and *Pseudomonas aeruginosa* was 18.6 ±0.52mm (*figure: 1.6*). Against fungi *Aspergillus niger* (*figure: 1.7*) and *Candida albicans (figure: 1.7)*, the inhibition zones measured were 6.6± 0.57 and 14.6± 0.56 mm respectively.

Qualitative and Quantitative screening

The Qualitative and Quantitative screening of phytochemicals present in *Aloe Vera Barbadensis* were performed with the extract, had shown the presence of varied range of active phytochemical components such as alkaloids, tannins, terpenoids, saponins, reducing sugars and Phenolic compounds.[63] *(Table: 1.4).* The quantitative analysis revealed that *Aloe Vera (Barbadensis)* comprises 23.83 ± 0.28 mg/g of alkaloid, 18.66 ± 0.57 mg/g of flavonoids, 14.26 ± 0.25 mg/g of phenolic compounds, 4.53 ± 0.3 mg/g of tannins and 13.5 ± 0.86 mg/g of Terpenoids shown in *Graph: 1.5.* Phytochemical components of *Aloe vera* are the biochemical compounds which are very much essential for the development of new drugs as they act as precursors. The major benefit of using *Aloe* gel extract for synthesis of silver nanoparticles is that easy availability, eco-friendliness, cost effectiveness and non-toxicity, have a wide range of metabolites that can aid these properties and are speedier than the microbes-based production. The main mechanism considered for the synthesis process is the existence of phytochemical compounds which are directly involved in reduction of silver ions and leads to formation of Ag-NPs. [63]

Characterization of Synthesized Ag-NPs

The characterization of silver nanoparticles synthesized by aqueous gel of *Aloe Vera (Barbadensis)* was done by U.V-vis-Spectrophotometer, TEM, XRD and FTIR analysis. The U.V vis-Spectrophotometer reveals the reduction of silver

ions into silver nanoparticles during exposure to *Aloe* gel by perceiving color change. The color change was mainly seen due to SPR (Surface Plasmon Resonance) phenomenon. The sharp peak of the SNP was observed at 420 nm. The absorbance was monitored after 1, 12, 24 and 48 hrs. of the reaction, which indicates the biosynthesis of SNP due to excitation of surface plasmon vibrations in these nanoparticles. The reduction of the metal ions completed up to 90% within 24 hrs. shown in *Graph: 1.13*. Further for the size and shape, TEM analysis followed by XRD was performed which revealed that the synthesized silver nanoparticles are ranging from 20-100 nm of spherical shape shown in *figure: 1.10*. The XRD had shown a typical peak around 38^0 indexing 111, which indicated the presence of cubic face-centered silver. It also suggested the crystalline structure of Silver nanoparticles and the broader peaks indicated the small particle size about 20-100 nm shown in *figure: 1.12*. The FTIR analysis was done for exploring types of biomolecules involved in synthesis and stabilization of silver nanoparticles. various peaks were observed at 3466.60 cm−1, 2098.58 cm−1, 1637.95 cm−1 and 677.08 cm−1 shown in figure: 1.11. The presence of bands at 3436.60 cm−1, corresponds to -N-H stretching of amide I which are mainly involved in capping and stabilizing of silver nanoparticles.

The peak was found at 1637.95 cm−1, identified as the C=C stretch of aromatic rings. Furthermore, the stretch for Ag-NPs was found around 677.08 to 412.04 cm−1. The FTIR results hence shows that the secondary structure of the proteins is not affected as a result of reaction with the Ag+ ions or binding with the silver nanoparticles. This analysis indicates that the phytochemical molecules could feasibly accomplish a purpose for the synthesis and stabilization of Silver nanoparticles in an aqueous medium. It is already stated carbonyl groups of amino acid residues and peptides from proteins have a strong attraction to bind with metal ions and hence protein acts as capping agents and defends the agitation process of nanoparticles. The band at 2098.58 cm-1 indicates presence of alkyne groups, as would be predictable due to plant origin specimens. The Carbonyl groups indicated the absorption of Terpenoids on the surface of metal nanoparticles and the presence of reducing sugars in the solution could be responsible for reduction of metal ions into nanoparticles. Synthesis of silver nanoparticles from gel extract of *Aloe vera* plant were confirmed by using different characterization techniques such as U.V-vis spectra indicated typical peak of Ag-NPs at 420 nm, TEM analysis resulted the size varied from 20-100 nm*(figure:1.12),* XRD shown the typical peaks at 111,200,220,311 indicates the presence of silver and FTIR analysis reveals the biochemical involved in synthesis of silver nanoparticles.

Figures, Tables & Graphs

Many researchers have explored several green routes for the synthesis but the application of this method is, it's a cost-effective, less time consuming, along with that the nanoparticle synthesized are biocompatible and non-toxic. Many prokaryotes and eukaryote have been explored for the production of silver nanoparticles but this method proven that, the use of Aloe Vera extract is one of the safest and effective one [58,65]. In comparison with other techniques, the chemical and physical properties of these nanoparticles may be same but the biological activity may differ significantly. Although, the biological medium used for the synthesis of nanoparticles are composed of similar or same active ingredients, still the antimicrobial effects might fluctuate substantially [55,58,60]. Aloe Vera leaf extract gel was processed with silver nitrate for the production of aloe-based silver nanoparticles. This was a microwaved based hydro-thermal method based of the principle of reduction reaction [59]. Additionally, the antimicrobial efficacy against pathogenic microbial strains of these produced hybrid silver-nano was checked and found effective [55]. This article was mainly emphasized on synthesis Ag-NPs using *Aloe Vera* gel extract. The colour of reaction between Silver nitrate and Gel mixture turned from pale yellow to dark brown after overnight incubation. of reaction, indicating reduction of Ag-NO_3 into Silver Nanoparticles [58,61,62].

Similar results were also observed that some researchers by using *Parthenium* leaf extracts; by using *Emblica officinalis* fruit extract; using whole *Aloe Vera* plant extract. [17,21,26,43] Usually, plant based natural extracts comprises numerous of active components, which have properties to reduce and stabilize the produced silver nanoparticles [57] Similarly, some researches also explored, green synthesis methods for production of silver nanoparticles by using Coffea arabica seed extract and also evaluated its antibacterial efficacy against different gram positive and gram

negative organisms [57,61]. As, it is little challenging to categorize all responsible chemicals of extracts; however, based on aforementioned studies the significant phytochemicals which may be accountable for altering silver ions into silver nanoparticles, could be alkaloids, terpenoids, phenolics, tannins, coumarins, glycosides, and ubiquinones [62]. Also, along with all these components, some proteins and their carbonyl groups of extract, also perform similar functions [56,57,64]. The Synthesis of silver nanoparticles in the reaction mixture was further confirmed by UV-Vis Spectroscopy. The UV-Visible spectra showed an absorption band at 420 nm (*graph 1.13.)* which corresponds to the absorbance of silver nanoparticles. UV- Visible spectroscopy is an important technique to determine the formation and stability of metal nanoparticles in aqueous solution. Some researchers also reported that *Vitex negundo* leaf extract showed absorption band at 420 nm [7,50,56].

Along with that some researches also reported that UV- Spectra noted high peak at 430 nm when green synthesis of silver nanoparticles was produced from aqueous stem bark extract of *Shorea Tumbuggaia* [16,56,58]. TEM results provided the information about morphology and size of the silver nanoparticles (*Figure 1.12*). The shape of the silver nanoparticles was found to be spherical. The average particle size was identified as 20-100 nm. Further TEM image showed the high density of silver nanoparticles and confirmed the synthesis of silver nanoparticles by the calculation of XRD analysis. Researchers also reported that the TEM image showed that the synthesized silver nanoparticles were cluster and mainly Spherical in shape [9,30,42,58]. The XRD data showed 2θ intense values with various degrees and results are corresponds to (111), (200), (220) and 311 Bragg's reflection based silver Nanoparticles; the XRD pattern with the diffraction peaks at 111, 200, 142, 220, and 311 planes for silver [9,30,42,58]. The outcome of these results clearly demonstrates that the Aloe leaf extract (gel) used for reduction and stabilization of Silver metal ions have an important role in synthesis of nanoparticles [58]. *Aloe Vera* and silver both were well known from ancient time for their inhibitory effects towards many bacterial and fungal strains commonly present in medical processes [58,64]. If silver is transformed into nanoparticles or nano-tools, its antimicrobial potential increases and effectively eliminates microbes [53,54,55].

CONCLUSION

The rapid Silver nanoparticles were synthesized by using aqueous based gel of well-known medicinal plant *Aloe Vera*. The synthesized nanoparticles were spherical in shape with approximately 20-100 nm of size. The bigger sized nanoparticles were observed due to its attachment with proteins and metabolites such as terpenoids with a function group of amines etc. of *Aloe* Vera. Further characterization of silver nanoparticles was completed by XRD, UV vis spectrometry, FTIR and TEM analysis. The metabolite of *Aloe Vera* plant act as stabilizing agents and prevents aggregation of silver nanoparticles and stabilizes it for a long time. Morphology and yield of nanoparticles can be controlled by monitoring reaction parameters such as time, pH etc. *Aloe Vera* was well known for its medicinal values which were enhanced by silver nano tools. *Aloe* based silver nanoparticles are equally effective against Gram positive and negative organisms.

The Chemical and physical methods for producing silver nanoparticles were being used over the years, but they are found to be toxic and tedious whereas green synthesis silver nanoparticles are more ecofriendly and easier. Further we confirmed the significance of Ag-NPs in the medical field as it shows excellent antibacterial activity against numerous microorganisms. This work contributed to a novel and unique feature of nano materials as an alternative antibacterial and fungicide agent for future. *Aloe Vera* along with Ag-NPs along can also increase its nutraceutical potential in resisting the multidrug-resistant pathogens. *Aloe* based Silver nanoparticles are very promising as future novel Nano medications. If plant extracts are used to make silver nanoparticles it will be low cost, environmentally friendly and easily scaled up. Plant induced synthesis of silver nanoparticles is the most suitable method because it does not leave any toxic contaminants. The applications of silver nanoparticles are diverse and numerous, but the major contribution is in food supplements, antimicrobial textiles, nutraceuticals, cosmetics and medical advice, bioremediation etc.

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Table 1: Biogenesis of Silver nanoparticles utilizing botanicals as coping agents or reducing with their size and shape.

S. NO	PLANT	PARTS USED	SIZE/SHAPE
1	*Pelargonium graveolens*	Leaves	16 to 40 nm
2	*Cinnamon zeylanicum*	Bark	31 and 40/ rod-shaped
3	*Chaetomorphalinum*	Whole plant	3 to 44 nm (average 30 nm)
4	*Aloe vera*	Pulp	25/ spherical
5	*Eclipta*	Leaves	2-6 nm
6	*Cycas*	Leaves	3.29 nm
7	*Jatropha curcas*	Latex	30-50 nm
8	*Cinnamon zeylanicum*	Bark	31-40 nm/ rod-shaped
9	Black Tea	Leaves	20 nm
10	*Ipomoea aquatica*	Leaves	100 – 400 nm spherical and cubic
11	*Enhydra fluctuans*	Leaves	100 – 400 nm spherical and cubic
12	*Ludwigiaadscendens*	Leaves	100 – 400 nm spherical and cubic
13	*Murrayakoenigii*	Leaves	20 nm/ hexagonal - spherical
14	*Citrus limon*	Juice	Below 50 nm
15	*Coriandrum sativum*	Leaves	26 spherical
16	*Gliricidiasepium*	Leaves	27 nm/spherical
17	*Jatropha curcas*	seeds	15 to 50 nm
18	*Capsicum annuum*	Leaves	10-12 nm
19	*Medicago sativa*	Leaves	Spherical 2–20 nm
20	Quercetin	Leaves	Radius 1–1.5 mm
21	Rice paper plant stem	Stem	Below 100 nm

22	*Aloe vera*	Leaves	50-50 nm /Triangular, spherical
23	*Emblica officinalis*	Leaves	10–20 nm, 15–25 nm
24	*Azadirachtaindica*	Leaves	50–100 nm
25	*Cinnamommumcamphora*	Leaves	Triangular, spherical 55–80 nm

Table 2: Qualitative and quantitative phytochemical screening of active compounds in Aloe barbadensis. Values are mean ± SD, (n=3)

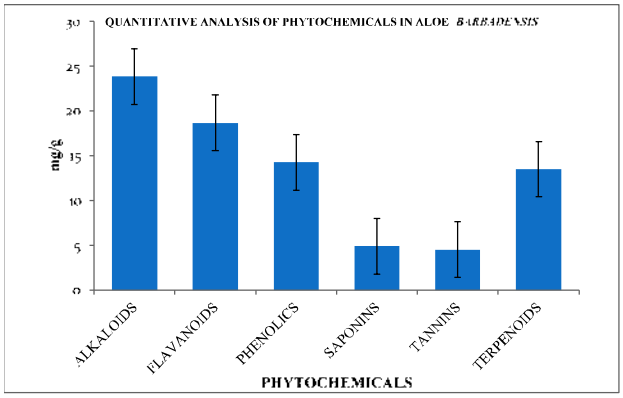
PHYTOCHEMICAL COMPOUNDS	QUANTITATIVE ANALYSIS	QUALITATIVE ANALYSIS
Alkaloids	+	23.83 ± 0.28 mg/g
Flavonoids	+	18.66 ± 0.57 mg/g
Phenolic compounds	+	14.26 ± 0.25 mg/g
Reducing sugars	+	Present
Saponins	+	5.3± 0.3 mg/g
Tannins	+	4.53 ± 0.3 mg/g
Terpenoids	+	13.5 ± 0.86 mg/g

Table 3: Antimicrobial evaluation of silver nanoparticles synthesized by Aloe Vera with inhibition zone (dia in mm) and SD values. Values are mean ± SD, (n=3)

Micro-organisms	Zone of inhibition (Dia in mm)	*Aloe Vera* gel (Negative control) (Dia in mm)
Staphylococcus aureus	19.33 ± 0.57	6
Bacillus cereus	15.3 ± 0.57	6
Pseudomonas aeruginosa	18.66 ± 0.52	6
Klebsiella pneumonia	13.66± 1.52	6
Aspergillus niger	6.66± 0.57	6
Candida albicans	14.6 ± 0.56	6

Figure 1: Morphological view of *Aloe Vera* (Barbadensis species).

Figure 2: SNP synthesized by *Aloe Vera* aqueous gel extract after incubation of 48 hours at room temperature.



Graph 3: Quantitative analysis of phytochemicals in extracts of Aloe specie.

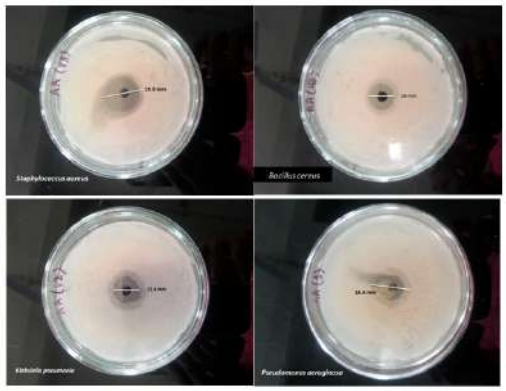
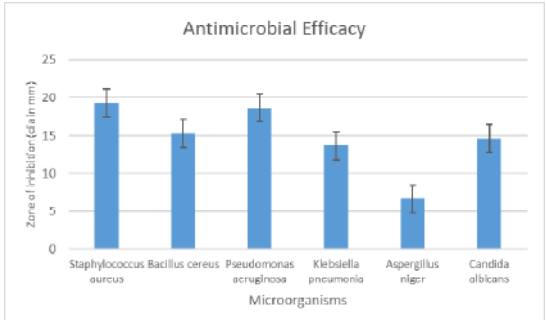


Figure 4: Antimicrobial efficacy of Aloe based silver nanoparticles against *Staphylococcus aureus*, *B. cereus*, *Klebsiella pneumonia*, and *Pseudomonas aeruginosa*, on MH agar plate after 24 hours of incubation at 37 °C.

Figure 5: Antimicrobial efficacy of Aloe based silver nanoparticles against *Aspergillus niger* and *Candida albicans* on SDA plate after 24-48 hours of incubation at 27 °C.



Graph 6: Graphical representation of antimicrobial efficacy of Aloe based silver nanoparticles.

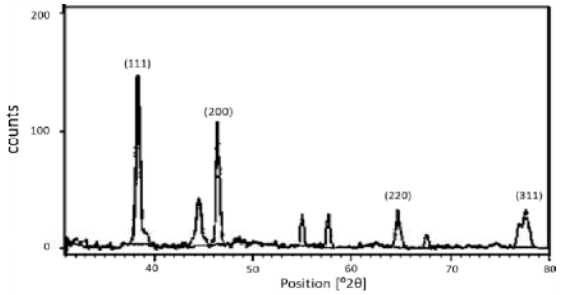


Figure 7: XRD results of Silver nanoparticles synthesized by Aloe Vera gel. The XRD data showed 2θ intense values with various degrees and results are corresponds to (111), (200), (220) and 311 Bragg's reflection-based silver Nanoparticles; the XRD pattern with the diffraction peaks at 111, 200, 220, and 311 planes for silver.

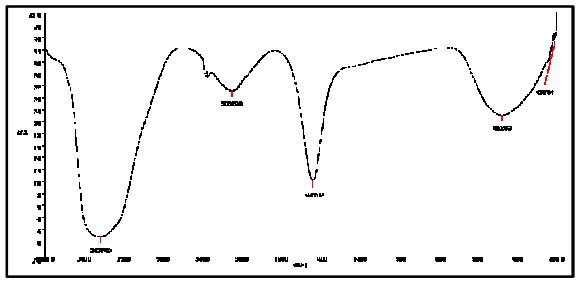


Figure 8: FTIR results of Silver nanoparticles synthesized by Aloe Vera gel. The presence of bands at 3436.60 cm–1, corresponds to **-N-H stretching of amide I which are mainly involved in capping and stabilizing of silver nanoparticles. The peak was found at 1637.95 cm–1,** identified as the C=C stretch **of aromatic rings. Furthermore, the stretch for Ag-NPs was found around 677.08 to 412.04 cm–1.**

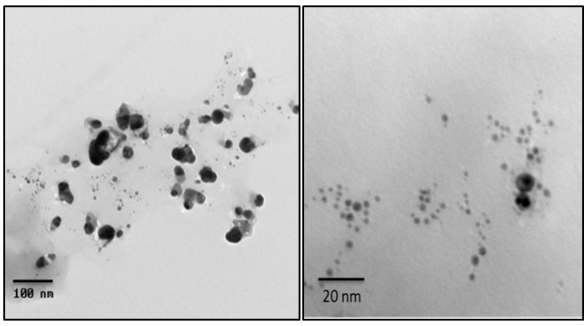
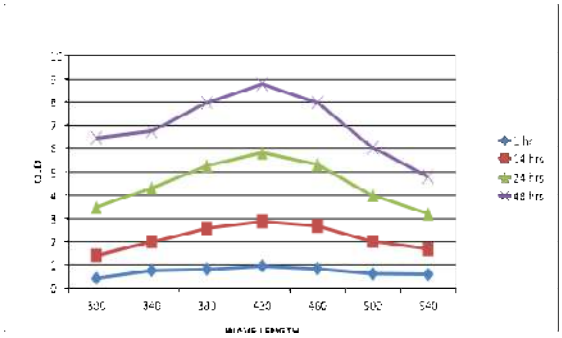


Figure 9: Transmission Electron Microscopy results showing Silver nanoparticles of 20-100nm synthesized by using *Aloe Vera* (Barbadensis species) gel extract.



Graph 10: U.V-vis spectrophotometry results of Silver nanoparticles synthesized by Aloe Vera gel. The sharp peak of the silver nanoparticle was observed at 420 nm. The absorbance was monitored after 1, 12, 24 and 48 hours of the reaction, indicating the formation of silver nanoparticles due to excitation of Surface Plasmon vibrations in silver nanoparticles.

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RESEARCH ARTICLE

Self-Microemulsifying Drug Delivery System: An Attractive Strategy for Enhanced Therapeutic Profile

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ABSTRACT

Solubility of orally administered drug is major challenge of pharmaceutical industry as nearly 35-40% of newly launched drugs possess low aqueous solubility which leads to their poor dissolution and low bioavailability, resulting in high intra & inter subject variability & lack of dose proportionality. This can be increased by different methods like salt formation, solid dispersion and complex formation. Self-Emulsifying Drug Delivery System (SEDDS) is gaining popularity for improving the solubility of lipophilic drugs. SEDDS are defined as isotropic mixtures of one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. Present review provides an updated account of advancements in SEDDS with regard to its composition, evaluation, different dosage forms and newer techniques to convert liquid SEDDS to solid and also various applications. Thus, only very specific pharmaceutical excipient combinations will lead to efficient self-microemulsifying systems. The fact that almost 40% of the new drug compounds are hydrophobic in nature implies that studies with SMEDDS will continue, and more drug compounds formulated as SMEDDS will reach the pharmaceutical market in the future.

Keywords: Self-microemulsifying drug delivery systems (SMEDDSs), Droplet Size, Oral Bioavailability, Lipophillic compound.

INTRODUCTION

Self-microemulsifying drug delivery system (SMEDDS) are described as isotropic mixtures of herbal or artificial oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents, and cosolvents/surfactants which have a completely specific ability of form fine oil- in-water (o/w) micro emulsions on to change stirring through dilution in aqueous media, along with gastrointestinal (gi) fluids. Various strategies are used to enhance oral bioavailability of weakly water soluble drugs. SEDDS are used to remedy low bioavailability problems of poorly soluble & highly permeable compounds. Self-emulsification occurs when the strength involvement with inside the dispersion is more than the strength required for the formation of droplets. The free strength of traditional emulsion could be very high as high strength is needed to form new surface between immiscible stages like oil and water. When SEDDS system is released with inside the lumen of the gastrointestinal tract, they arrive in touch with gi fluid and form a fine emulsion (micro/ nano) so referred to as as in situ emulsification or self-emulsification which in addition ends in solubilization of drug that may ultimately be

absorbed through lymphatic pathways, bypassing the hepatic first-pass effect. Lipid primarily based totally formulations provide a extensive form of formulations like solutions, suspensions, solid dispersions and self- micro emulsifying drug delivery systems (smedds).

- Inhibition of cellular efflux mechanisms, which hold drugs out of circulation.
- Formulation of fine dispersions and miscellar suspensions to block aggregation and re-crystallization of the drug components.
- Ability of positive lipid compounds and their metabolites to provoke modifications with inside the gastrointestinal fluid to want advanced drug absorption.
- Certain lipid excipients are related to selective drug uptake into the lymphatic delivery system, thereby decreasing the impact of first pass drug metabolism with inside the liver.

Approximately 40% of recent drug applicants have poor water solubility and the oral delivery of such drugs is often related to low bioavailability, excessive intra- and intersubject variability, and a loss of dose proportionality. To conquer those problems, diverse system techniques are exploited which include the usage of surfactants, lipids, permeation enhancers, micronisation, salt formation, cyclodextrins, nanoparticles and solid dispersions . Recently, a good deal interest has been paid to lipid-primarily based totally formulations with specific emphasis on self-emulsifying drug delivery systems (sedds) to enhance the oral bioavailability of lipophilic drugs.(4,5,6)

Self-nano emulsifying drug delivery system (snedds):(7)

- Snedds are nano-emulsions formed with the aid of using sedds. They are heterogeneous dispersions of immiscible liquids (oil-in-water [o/w] or water-in-oil [w/o]) having a mean droplet length withinside the nanometric scale (generally twenty–two hundred nm), irrespective of technique of preparation
- This is mainly essential for tablets for increasing the solubility inclusive of simvastatin, atorvastatin.

Self-micro emulsifying drug delivery system (smedds):(8)

- Smedds are micro-emulsions formed with the aid of using the sedds. It is thermodynamically solid and forms optically transparent emulsion.
- The important distinction among micro-emulsions and not unusual place emulsions is specially because of particle size of droplets.
- The size of the droplets of not unusual place emulsion levels among 0.2 and 10 μm, and that of the droplets of micro-emulsion formed with the aid of using the smedds normally levels among 2 and 100 nm. Since the particle size is small, the entire surface region for absorption and dispersion is considerably large than that of solid dosage form and it is able to without problems penetrate the gastrointestinal tract and be absorbed.

PROPERTIES OF SEDDS :(9,10,11)

1. They are capable of self-emulsify rapidly in gastro-intestinal fluids & below the affect of mild agitation supplied with the aid of using peristaltic and different actions of gastro intestinal tract, they form a fine o/w emulsion.
2. They can efficiently include drug (hydrophobic or hydrophilic) in the oil surfactant mixture.
3. They may be used for liquid in addition to solid dosage forms.
4. They require decrease dose of drug with recognize to standard dosage forms.

ADVANTAGES OF SELF-EMULSIFYING DRUG DELIVERY SYSTEM: (11,12)

- Improvement in oral bioavailability through enhancing solubility and efficient drug transport.
- Reduction in inter- and intra-concern variability and meals effects.
- Ability to supply peptides which might be at risk of enzymatic hydrolysis in git.
- No impact of lipid digestion method not like the opposite lipid-based drug transport systems.
- When polymer is integrated with inside the composition of smedds, it offers extended release of medicament
- Fine oil droplets of smedds might pass hastily facilitating extensive distribution of the drug in the course of the stomach and sell extensive distribution of the drug during the gi tract, thereby decreasing the irritation frequently come across throughout prolonged contact between bulk drug substance and the intestine wall.
- Emulsions are touchy and metastable dispersed forms at the same time as smedds are physically strong formulations.
- As in comparison with oily solutions, they offer a big interfacial region for partitioning of the drug among oil and water.
- Ease of manufacture and scale- up is one of the maximum critical benefits that make smedds specific while in comparison to different drug delivery systems like solid dispersions, liposome, nanoparticles, etc., as they require quite simple and reasonably priced production facilities like easy mixer with agitator and volumetric liquid filling system for large- scale production.

DISADVANTAGES OF SMEDDS: (12,13)

- Lack of appropriate predicative in vitro fashions for evaluation of the formulations.
- Further improvement can be primarily based totally on in vitro - in vivo correlations and consequently exclusive prototype lipid-primarily based totally formulations desires to be evolved and examined in vivo in a appropriate animal model.
- Another is chemical instabilities of medication and excessive surfactant concentrations in formulations (about 30-60%) which aggravate git.
- The sedimentation propensity of the drug on dilution can be increase, due to the dilution effect of the hydrophilic solvent
- Formulations containing numerous additives grow to be extra tough to validate.
- High manufacturing costs.
- Low drug incompatibility.
- Drug leakage. So it can permit much less drug loading

MECHANISM OF SMEDD :(14,15)

The emulsion is stabilized through the surfactant molecules that form a film across the inner section droplet. In case of smedds, the free energy of formation could be very low and positive or maybe negative which ends up in thermodynamic spontaneous emulsification. It has been counseled that self-emulsification takes place because of penetration of water into the liquid crystalline (lc) segment this is formed on the oil/surfactant-water interface into which water can penetrate assisted through mild agitation all through self-emulsification. After water penetrates to a sure extent, there may be disruption of the interface and a droplet formation.. This lc segment is taken into consideration to be liable for the high stability of the ensuing microemulsion towards coalesce.

FORMULATION COMPONENTS OF SMEDDS: (16.17,18)

1. Active pharmaceutical ingredient
2. Oil
3. Surfactant
4. Co-surfactant
5. Co-solvents
6. Other components.

Active pharmaceutical ingredient (api):

Drug must be soluble in oil phase as this impact the capacity of smedds to maintain the api in solubilized form. Lipophilic drugs, which includes cinnarizine with log p>5, are desirable candidate for smedds. As, sedds are used to growth the solubility of poor water-soluble drugs, bcs class ii drugs are favored e.g. Nifedipine, , simvastatin, danazol, ketoconazole, naproxen, carbamazepine, Itraconazole, vitamin e, mefanimic acid,

Oil

Oil is the maximum vital excipient withinside the method of smedds because it solubilizes the lipophilic drug in required quantity. The primary criterion for deciding on the oil is that the drug must have high solubility in it, so this may decrease the extent of the method for the delivery of efficient dose.

Surfactant

- Anionic surfactants, wherein the hydrophilic organization consists of a negative rate. Examples: potassium laurate, sodium lauryl sulfate.
- Cationic surfactants, wherein the hydrophilic organization consists of a positive rate. Example: quaternary ammonium halide.
- Ampholytic surfactants (zwitterionic surfactants) comprise each a negative and a positive rate.Example: sulfobetaines.
- Nonionic surfactants, wherein the hydrophilic organization consists of no rate however derives its water solubility from highly polar groups. Examples: sorbitan esters (spans), polysorbates (tweens).

Co-surfactant

The formulation of an optimum smedds requires incredibly more concentrations (usually greater than 30% w/w) of surfactants it may leads to reasons gi irritation. So co surfactant is used to lessen awareness of surfactant. Role of the co- surfactant collectively with the surfactant is to decrease the interfacial anxiety to a totally small even temporary negative value. At this value the interface could enlarge to form fine dispersed droplets, and eventually adsorb greater surfactant and surfactant/co-surfactant till their bulk situation is depleted sufficient to make interfacial tension positive again. This method regarded as 'spontaneous emulsification' forms the micro emulsions. For the formulation of an ideal smedds, extreme concentration of surfactant is required to lessen interfacial tension sufficiently, which leads harmful, so co-surfactants are used to lessen the concentration of surfactants. In general, co-surfactant of hlb value 10-14 is used inclusive of ethanol, propylene glycol, polyethylene glycol.

Co-solvents

Organic solvents allow the dissolution of large quantities of both the hydrophilic surfactant or the drug in oil phase. For eg: butanol, ethanol, propylene glycol, etc., tributyl citrate and amides as 2-pyrolidine, esters inclusive of ethyl propionatecaprolactum, and PVP

Other components.

Viscosity enhancers

The viscosity of the emulsions may be changed with the help of using the usage of more material inclusive of acetyl alcohol, tragacanth, beeswax and stearic acids etc.

Polymers

Polymer matrix (inert) found in 5 to 40% w/w, which isn't ionizable at physiological ph are capable of form matrix. For eg: ethyl cellulose, HPMC etc.

Antioxidant agents

Lipophilic antioxidants (e.g. A tocopherol, propyl gallate, ascorbic palmitate) stabilize the oily content material of sedds formulations.

CONSTRUCTION OF PHASE DIAGRAM: (19,20)

Phase diagrams have been constructed to achieve the percentage of additives which could bring about maximum micro emulsion life area. These diagrams have been constructed with oil, surfactant/co-surfactant and water the usage of water titration approach at room temperature. The technique consisted of preparing solutions of various ratio of surfactant to co-surfactant with the aid of using weight inclusive of 1:1, 2:1, 3:1, etc., those solutions then vortexed for five mins and located at 50°c for 1 hr in order that an isotropic combination become obtained. Each of those solutions become then used for making ready a mixture containing oil and smix (mixture of surfactant and co-surfactant) in the following ratios with the aid of using weight: 1:9, 2:8, 3:7, 4:6, 5:5, 6:4,7:3, 8:2, 9:1 and after preparation vortexed for five mins observed with the aid of using putting in oven at 50°c for 1 hr. All the combinations have been then located at room temperature for twenty-four hrs. Water from 5% to 95% of the combination become delivered at 10-15 mins interval to every of the mixture below stirring on magnetic stirrer. After every addition, the mixtures have been located for their appearance (turbid or clean). Turbidity of the samples could suggest the formation of a coarse emulsion, while a clean isotropic solution could suggest the formation of a microemulsion. Percentage of oil, smix, and water at which clean mixture become formed have been selected, and the values have been used to prepare ternary.

PREPARATION OF SMEDDS:(18,19,20,22)

From the ternary phase, diagram ratio of surfactant to co-surfactant become optimized. Then with the aid of using various ratio of oil to smix, specific formulations have been organized with and with out the drug. Formulations have been organized with the aid of using making ready optimized ratio of smix first, for this surfactant and co-surfactant have been as it should be weighed after which vortexed for 5-10 mins. After that, smix become placed in an oven at 50°c for 1 hr. Oil with perticular ratio are transport to smix , these preparation have been vortexed for 5-10 mins and kept in an oven at 50°c for 1 hr ,then it should be formed isotropic mixture . Drug are loaded to the isotropic formulations on the end and vortexed with the help of using vortex shaker till clear solution become formed

EVALUATION OF SEDDS: (21,22,23)

Drug Content

Drug from pre-weighed SEDDS is extracted with the aid of using dissolving in appropriate solvent. Drug content material in the solvent extract is analyzed with the aid of using appropriate analytical technique.

Dispersibility Test

The dispersibility test of SEDDS is formed to assess to dissolved into emulsion and classof the size of make certain globules. It is carried with the aid of using the usage of a standard USP dissolution equipment (Paddle Type). One ml of every method is added to 500 ml of water at 37 + 0.5ºc and the paddle is rotated at 50 rpm. It should be titration with the aid of water the SEDDS preparation forms a mixture or gel that is of several type depends upon the in vitro whole preparation of method may be assessed the usage of the following grading system. Grade A: Rapidly forming (inside 1 min) nanoemulsion, having a clear or bluish appear.

Grade B: quickly obtain, moderately less clean emulsion, having a bluish white appearing.

Grade C: pure milky emulsion are formed inside within 2 min.

Grade D: diminish grayish white emulsion are moderately oily formaulation this is slow to emulsify (greater than 2 min).
Grade E: preparation occures both poor or minimal emulsification with huge oil globules present at the surface.
Grade A and Grade B method will continue to be as nano emulsion while dispersed in GIT. While method falling in Grade C might be recommend for SEDDS method.

Rheological properties determination

The SEDDS device also can be administered in soft gelatin capsules, in which, it should have considerable flow properties for processing. The rheological properties (viscosity, flow, thixotropy, static yield, creep value) of method (diluted to 5 % v/v water) are decided through rotational viscometers, digital contraptions coupled with either cup and bob or coaxial measuring device. A type of rotational viscometer has additionally been used for determination of viscosity of clean in addition to different SEDDS formulations which has been saved for longer period of time. Viscosity dedication of liquid SEDDS also shows whether or not the system is o/w or w/o, as low viscosity systems are o/w and excessive viscosity systems are generally w/o in nature. Viscosity of method is inversely proportional to dilution.

Thermodynamic stability research

The physical stability of a formulation could be required for its allover performance as it could be adversely affected through the aggregation of the drug in medium pattern. Poor physical stability of method can cause phase separation of excipients which impacts bioavailability in addition to therapeutic efficacy. Also the incompatibilities among method and gelatin shell of capsule (if method filled in capsule) might also additionally purpose brittleness, softness and behind schedule disintegration or incomplete release of drug. The following cycles are achieved for those research).

A. Heating cooling cycle: Six cycles of cooling and heating among fridge temperature (4°C) and extended temperature (45°C) with exposure at every temperature for now no longer much less than forty eight hours are carried. Those formulations, that are stable, are then subjected to centrifugation test.
B. Centrifugation:in this preparation are pass the heating cooling cycle are centrifuged at 3500 rpm for 30 min. Those formulations that don't display any phase separation are taken for the freeze thaw pressure test.
C. Freeze thaw pressure cycle: Three freeze thaw cycles b/w -21° C & 25° C with storage at every temperature for now no longer much less than the ones formulations which pass this test show properly stability without a phase separation, cracking or creaming. In this preparation that pass this assess are addition kept for dispersibility to assess for evaluation of self-emulsification efficiency.

Robustness to Dilution

Emulsions upon dilution with diverse dissolution media have to not display any phase separations or precipitation of drug even after 12 hrs of storage, such method is taken into consideration as strong to dilution.

Turbid Metric Evaluation

Turbidity is a parameter for dedication of droplet size and self-emulsification time 19 Fixed amount of SEDDS is introduced to constant amount of appropriate medium (0.1 N HCL or Phosphate Buffer) below non-stop stirring at 50 rpm on magnetic stirrer at most appropriate temperature and the turbidity is measured the usage of a turbidimeter. Since the time required for whole emulsification is too short, it isn't viable to screen the rate of alternate of turbidity i.e. Rate of emulsification. Turbidimetric assessment is done to monitor the growth of droplet after emulsification.

Droplet size analysis & Particle size measurements

Photon correlation spectroscopy (PCS) or dynamic light scattering (DLS) or Laser Diffraction Techniques are used to decide droplet size of emulsion. A quantity of equipmentsare to be had for measurement of particle length viz. Particle Size Analyzer, Mastersizer, Zetasizer etc. Which are capable of measure sizes among 10 and 5000 nm.

Self-Emulsification Time

The self- emulsification time is decided via way of means of the usage of USP dissolution equipment at 50 rpm, in which 0.5 g of SEDDS formulations is delivered into 250 ml of 0.1N HCL or 0.5% SLS (Sodium Lauryl Sulphate) solution.

***In vitro* Diffusion study**

This look at is accomplished to decide release conduct of method the usage of dialysis approach in which phosphate buffer (ph 6.8) is usually used as dialyzing medium 20. The different end of membrane is also tied with thread after which allowed to rotate in dialyzing medium at one hundred rpm the usage of magnetic stirrer or dissolution equipment. Samples are withdrawn at exclusive time durations after which after appropriate dilution are analyzed. Volume of samples withdrawn is changed with clean dialyzing medium.

***In vitro* Dissolution technique**

The quantitative in vitro dissolution research are finished to evaluate drug release from oil segment into aqueous section via way of means of USP type 2 dissolution equipment the usage of 500 ml of simulated gastric fluid containing 0.5% w/v of SLS at 50 rpm and retaining the temperature at 37±0.5ºc. Aliquots of samples are withdrawn at regular durations of time and extent withdrawn is replaced with clean medium. Samples taken are then analyzed via way of means of the usage of UV spectrophotometer or some other appropriate approach.

Liquefaction Time

This test is achievement to choose the time required via way of means of strong SEDDS method to soften in vivo in the non appear of stirring in induced gastric fluid. The method is packed in a obvious polyethylene film and tied to the bulb of thermometer. The thermometer is then located in spherical backside flask wherein simulated gastric fluid with out pepsin is filled. The temperature is maintained at 37±0.5ºc via way of means of the usage of heating mantle.

Refractive index (R.I.) & Percent Transmittance

Refractive Index & percentage transmittance are decided to test the transparency of method. Refractive Index of the method is measured via way of means of refractometer through setting drop of solution on slide & then evaluating with water (R.I = 1.333). The percentage transmittance of the formula is measured at a selected wavelength the usage of UV spectrophotometer via way of means of the usage of distilled water as blank.

FACTORS AFFECTING SMEDDS: (24,25)

Nature and dose of the drug

Drugs that are administered at very excessive dose aren't appropriate for smedds except they exhibit first-rate solubility in as a minimum one of the additives of smedds, preferably lipophilic phase. The drugs which exhibit restricted solubility in water and lipids usually with log p values of about 2 are maximum difficult to deliver via way of means of smedds. The capacity of smedds to keep the drug in solubilised form is substantially inspired via way of means of the solubility of the drug in oil phase.

Concentration of surfactant or co- surfactant

If surfactant or co-surfactant is contributing to the more quantity in drug solubilization then there might be a chance of precipitation, as dilution of smedds will cause decreasing of solvent capability of the surfactant or co-surfactant.

Polarity of the lipophilic phase

The polarity of the lipid phase is one of the elements that govern the drug release from the microemulsions. The polarity of the droplet is governed via way of means of the hlb, the chain duration and degree of unsaturation of the fatty acid, the molecular weight of micronized drug.

APPLICATIONS OF SMEDDS:(26,27,28,29)

Solubilization in smedds

Owing to their regularly excessive content material oil, in addition to of surfactant, smedds are normally efficient solubilizers of materials of a extensive variety of lipophilicity. Thus, the solubilizing capability of a w/o microemulsion for water soluble drugs is usually better than that of an o/w microemulsion, even as the opposite is real for oil soluble drugs. Furthermore, the solubilization depends at the smedds composition.

Sustain release from smedds

Due to the extensive variety of systems taking place in them, smedds show a wealthy conduct concerning the discharge of solubilized material. Thus in. Case of o/w microemulsion, hydrophobic drugs solubilized specifically in the oil droplets, experience hindered diffusion and are consequently released as a substitute slowly (depending at the oil/water partitioning of the substance). Water soluble drugs, on the opposite hand, diffuse basically with out obstruction (depending at the quantity fraction of the dispersed phase) and are release fast.

Increase the bioavailability of drug

Many of medication had been lipophilic in nature so, it need to be insoluble in water. Lipophilic drug need to have low bioavailability. In smedds, tablets need to be combining with the oil and make a complex. Oil is easily absorbed from the intestine and increase the solubility of medication. So enhance the bioavailability of the drug. Ex. Julianto et al, was growth the three fold bioavailability from sedds which consists of the tween eighty and palm oil.

Super saturable smedds

Super saturable-smedds were evolved to overcome the poisonous impact of surfactant or gi side outcomes produced via way of means of surfactant while utilized in very excessive concentration as usually utilized in smedds.

Protection from biodegradation:(30)

Drugs for which each solubility and degradation is low in the git make contributions to a low oral bioavailability, smedds is useful for such drugs because of the capacity to lessen degradation in addition to enhance absorption.

CONCLUSION

As according to the novel drug delivery system, smedds are a promising method for the method of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs which belongs to elegance ii may be made feasible via way of means of smeddss, that have been proven to extensively enhance oral bioavailability and for this reason the dose of the drug may be reduced. With future improvement of this technology, smeddss will hold to allow novel packages in drug transport and solve related to the transport of poorly soluble tablets.

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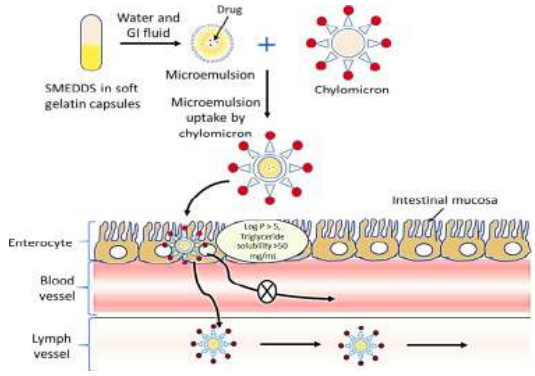

Fig.1.lymphatic pathways

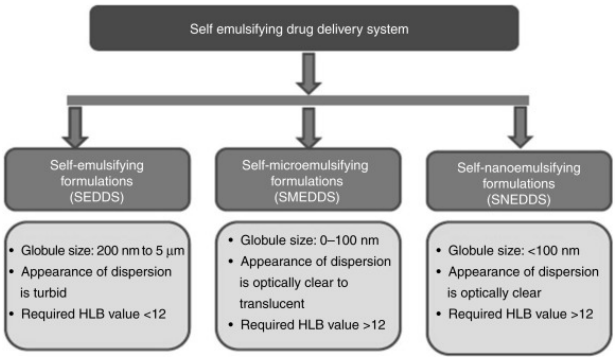

Fig.2.Self emulsifying drug delivery system

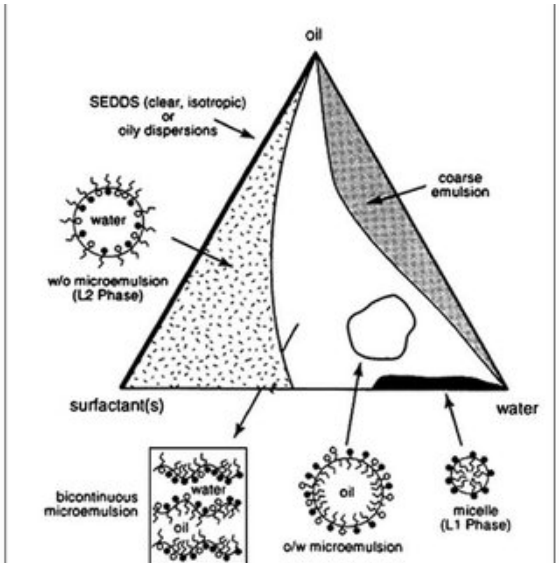

Fig.3.CONSTRUCTION OF PHASE DIAGRAM

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RESEARCH ARTICLE

Development and Validation of an LC-MS/MS Method for Estimation of Rivaroxaban in Human Plasma

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ABSTRACT

A simple and rapid liquid chromatography–tandem mass spectrometry (LC–MS/MS) method has been developed and validated for the determination of rivaroxaban in human plasma using rivaroxabanD4 as an internal standard (IS). The chromatographic separation was done using Phenomenex Luna-C18 column with isocratic flow of mobile phase composed of 0.2% formic acid in water and acetonitrile (60:40 %v/v) with a flow rate of 1 mL/min. The detection of rivaroxaban and rivaroxabanD4was performed using positive electrospray ionization, multiple reaction monitoring (MRM) transitions were set at 436.0/144.9 (m/z) and 440.0/144.9 (m/z) for rivaroxaban and rivaroxabanD4, respectively. The plasma samples containing analyte and IS were extracted using liquid-liquid extraction method. The method was fully validated for its selectivity, sensitivity, linearity, accuracy and precision, recovery, matrix effect and stability. The assay was linear over the concentration range of 0.509–609.286 ng/mL. The within andbetween run precision were ≤3.9% and ≤4.1%,respectively and accuracy were > 98.2% and > 97.9% respectively. This method is suitable for the quantification of rivaroxaban in human plasma samples for pharmacokinetics and bioequivalence studies of rivaroxaban tablets.

Keywords: Rivaroxaban, LC-MS/MS, Bioanalytical, Human plasma, Validation

INTRODUCTION

Rivaroxabanis an oral oxazolidinone-based anticoagulant, is a potent, selective, direct inhibitor of factor Xa that is used in the prevention of venous thromboembolism in adult patients after total hip replacement or total knee replacement surgery [1]. The potency of factor Xa inhibition occurs primarily as a result of rivaroxaban binding with high selectivity to the S1 and S4 pockets of the serine endopeptidase. Inhibition of factor Xa interrupts the intrinsic

and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi[2].Rivaroxaban does not inhibit thrombin (activated Factor II), and has no effects on platelets have been demonstrated [3]. Chemically, Rivaroxaban is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl) phenyl]-1, 3-oxazolidin-5-yl} methyl)-2-thiophenecarboxamide. Its structure is shown in Figure 1.

The literature described few publications on the use of LC-MS/MS and high-performance liquid chromatography (HPLC) for the detection and quantification of rivaroxaban alone [4-9] or combination with other direct oral anticoagulants [10-14] in human plasma. Most of these methods used protein precipitation as a sample cleanup or the method was less sensitive, protein precipitation does not remove phospholipids, which can build up on the analytical column and pollute the mass spectrometer source, and thereby contribute to matrix effects (MEs) and reduced sensitivity. One method was reported using solid-phase extraction [15] and it was a time consuming and expensive method.

In this report, we describe a simple and rapid liquid chromatography/tandem mass spectrometry (LC/MS/MS) method developed and validated for the quantification of rivaroxaban in human plasma using liquid-liquid extraction method. LC-MS/MS is the most widely used method for therapeutic monitoring and bioavailability studies of rivaroxaban due to very good sensitivity and selectivity, as well as adequate accuracy and precision. Compared to published methods, the current method is having advantage of less plasma volume was required, sample preparation was simpler and the analysis time was shorter to suitable to analyze large number of bioequivalence/Pharmacokinetic/therapeutic monitoring study samples. The method is extensively validated as per the USFDA Guidance for Industry: Bioanalytical method validation [16].

MATERIALS AND METHODS

Chemicals and Solvents

Rivaroxaban and rivaroxaban-d4 were obtained from Vivan Life science, India. HPLC-grade methanol, acetonitrile, methyl tertiary butyl ether and ethyl acetate were purchased from JT Baker (Phillipsburg, NJ, USA). HPLC LiChropur® gradeortho- phosphoric acid and Formic acid were purchased from Sigma-Aldrich™ (St. Louis, Missouri, USA). HPLC-grade water from a Milli-Q water system (Millipore, Bedford, MA, USA) was used. All other chemicals were of analytical grade.

LC–MS/MS Instrument Conditions

The liquid chromatography system from Shimadzu (Kyoto, Japan) wascomposed of a LC-10ADvp pump, an auto sampler (SIL-HTc), and an online degasser (DGU-14A). Chromatographic column used was Phenomenex Luna-C18 column (100 × 4.6 mm, 3μm) at column temperature of 40°C. Separation of analyte and IS was performed underisocratic condition at a flow rate of 1 mL/ min with split (1:1), the isocratic mobile phase was constituted of 40:60 v/v % of 0.2 % formic acid and acetonitrile. The auto sampler temperature was maintained at 4°C, and the injection volume was kept at25 μL and the total LC run time was 3.5 minutes.

Ionization and detection of analyte and IS were performed on a triple quadrupole mass spectrometer API 4000 (MDS SCIEX Toronto, Canada) equipped with an electro spray ionization (ESI) interface operating in the positive ion mode. Quantitation was done using MRM mode to monitor protonated precursor → product ion transition of m/z436.0 → 144.9 for analyte and 440.0 → 144.9 for IS. All the parameters of LC and MS were controlled by Analyst software version 1.4.2. The source dependent parameters for analyte and IS maintained were curtain gas (CUR) 30 psi, ionization voltage (IS): 5500 V, temperature (TEM): 500°C, nebulizer gas (GS1) 45 psi, heater gas (GS2) 55, collision gas (CAD) 8.

The compound dependent parameters for analyte and IS were maintained declustering potential (DP) 90, entrance potential (EP) 10, collision energy (CE)35, and collision cell exit potential (CXP) 9,quadrupole 1 and quadrupole 3 were maintained at unit resolution and dwell time set was 400 msec.

Preparation of standard and quality control (QC) samples

A stock solution (220.75µg/mL) of rivaroxaban was prepared using acetonitrile. The stock solution were diluted further to produce standard solutions with concentrations range about 25.431 ng/mL to 30464.30 ng/mL using acetonitrile: water 50:50 %v/v. Quality control (QC) solutions were prepared independently at low, medium, and high concentrations (69.688, 10754.304 and 23378.925 ng/mL) in the same way. A 20µL aliquot of each standard solution was mixed with 980µL of pooled plasma to produce calibration standards of rivaroxaban with concentration range about 0.509 ng/mL to 609.286 ng/mL. QC samples (1.394, 215.086 and 467.579 ng/mL) were generated from QC solutions with the same procedure. A stock solution (204.026µg/mL) of rivaroxabanD4 was prepared with acetonitrile and diluted with acetonitrile: water 50:50 % v/v to give a final concentration of 102.013 ng/mL. The stock and working solutions were stored at 2-8°C and the spiked plasma samples were stored in a -20 °C freezer.

Sample Preparation

The spiked plasma samples were retrieved from the deep freezer and thawed in a water batch at room temperature. The thawed samples were vortexed for complete mixing. A 50 µL of IS was added in to pre-labeled polypropylene tubes except in blank samples wherein 50 µL of dilution solution was added to compensate. A 100 µL of samples were transferred into it and vortexed, then 100 µL of ortho-phosphoric acid and 2 mL organic solvent mixture of ethyl acetate and methyl tertiary butyl ether (MTBE) in ratio of 80:20 v/v %was added and vortexed for about 5 minutes, then the samples were centrifuged for 5 min at about 4000 rpm maintained at temperature 4°C. After centrifuge 1.6 mL of supernatant was transferred into prelabeled glass tubes. The supernatant was dried at 40°C under a stream of nitrogen. The dried residue was reconstituted with 0.5 mL of mobile phase and transferred into auto sampler glass vials and injected in to LC-MS/MS system.

BIOANALYTICAL METHOD VALIDATION

Method validation was performed according to USFDA Guidance for Industry, Bioanalytical Method Validation (US Food and Drug Administration, 2018) [11]. Selectivity was assessed by comparing chromatograms of spiked plasma samples in the lower limit of quantification (LLOQ) concentration with plasma from six different individuals and lipemic plasma. A calibration curve in the range of 0.509 to 609.286 ng/ml was evaluated using the assay of three independent analytical curves on 3 different days by weighted linear regression ($1/x^2$) of analyte / IS peak area ratios. LLOQ was defined as the lowest concentration of analyte that could be quantitatively determined with precision of ≤ 20% and accuracy of 80-120%. The accuracy and precision were determined by assay of low, medium, and high quality control samples on different days. The intraday and interday precisions were required to be lower than 15% and the accuracy to be within ± 15%, except at LLOQ, where it should not exceed 20%.

Recovery was determined by comparing the mean peak areas for six replicate analysis of low, medium, and high QC samples with those of blank plasma extracts reconstituted with the corresponding QC solutions. Recovery of the analyte need not be 100%, but the extent of recovery of an analyte and the internal standard should be consistent, precise, and reproducible. Matrix effects can be described as the difference between the mass spectrometric response for an analyte in standard solution and the response for the same analyte in a biological matrix. Matrix effect was assessed by employing six independent lots of analyte free matrix for the preparation of each of the low and high QC samples. Three replicates at each of the low and high QC sample concentration levels were assayed for each matrix lot [12-13].

The stability of the analyte and IS in human plasma under different temperature and timing conditions, as well as their stability in the stock solutions were evaluated. QC samples were subjected to short-term room temperature

conditions, to long-term storage conditions (-20°C), and to freeze/thaw stability studies. All the stability studies were conducted at low and high QC concentration levelswith six determinations for each.

RESULTS AND DISCUSSION

Mass spectrometry and Chromatography

The most abundant product ion of each analyte was selected for MRM monitoring. In both analytes, protonated molecule $[M+H]^+$ was monitored in electrospray positive ionization mode. Therefore, the ion transitions m/z 436.0>144.9 and 440.0>144.9 were selected for MRM of the rivaroxaban and rivaroxaban D4, respectively. HPLC was used as separation method for the analysis of rivaroxaban and rivaroxaban D4. The chromatographic conditions were investigated on several different reversed phase columns (Phenomenex Luna, Zorbax SB C_{18}, Kinetex C_{18}) to obtain a suitable retention time and symmetrical peak shape[14]. To get the shortest analysis time and avoid the matrix effects, different percentages of mobile phase composition and flow rate were tested. In early experiments 0.1% formic acid and acetonitrile30:70 v/v % was used as a mobile phase with 0.8 mL/min flow rate but the signal and peak shape was not good, in order to achieve good peak shape and desired sensitivity with good signal to noise ratio 0.2% formic acid and acetonitrile 40:60 v/v% was used as mobile phase. On the other hand these changes greatly increased the running time, to reduce the running time the mobile phase flow was increased to 1.0 mL/min with a split ratio of 1:1 (MS/MS: waste). This last condition allowed a running time of 3.5 min with desired peak response at LLOQ concentration. The best peak shape and retention time were achieved using Phenomenex Luna column (100 x 4.6 mm, 3µm)at a column temperature of 40°C.

Sample preparation

Different methods of sample preparation including protein precipitation, solid phase extraction (SPE) and liquid-liquid extraction (LLE) with various organic solvents (such as methyl tert-butyl ether, ethyl acetate, dichloromethane, hexane, and chloroform) were evaluated. Protein precipitation introduces serious matrix effects, besides a dirty extract may damage the equipment during bioanalytical routine, SPE required lengthy extraction procedure and recovery also very low when compared with liquid-liquid extraction. Aconsistent, reproducible recoveries, desired sensitivity and less matrix effect were obtained by liquid- liquid extraction method using mixture of ethyl acetate and methyl tertiary butyl ether in ratio of 80:20 v/v %.

Assay validation

Selectivity and sensitivity

Assay selectivity was performed to evaluate any interference from endogenous matrix. Different lots of drug-free plasma samples (normal, hemolysed and lipemic) together with spiked plasma of rivaroxaban at lower limit of quantification level (LLOQ = 0.518 ng/mL) were processed and analyzed. No significant interference from endogenous components was observed at retention time of analyte and IS in all tested human plasma. Figure 2 shows typical MRM chromatograms of blank human plasma.

The sensitivity was evaluated in terms of LLOQ (defined as the lowest concentration that could be analyzed with acceptable accuracy and precision), the obtained LLOQ was 0.518ng/mL with a mean accuracy of 98.60 % and a mean precision of 5.11%. Figure 3 shows typical MRM chromatogram of LLOQ, the chromatograms show excellent peak shape for both the analyte and the IS, the retention times were short enough to allow a run time of 3.5 min, which is suitable for routine analysis.

Linearity

The eight point calibration curve obtained using weighted linear regression ($1/x^2$) showed good linearity over the whole concentration range (0.509 to 609.286 ng/mL), which covered the concentrations found in human plasma after administration of rivaroxaban in this bioequivalence study. The correlation coefficient was better than 0.99. The least-squares linear regression was used to mathematically define the calibration curve. This was especially important because a wide calibration range was selected.

Accuracy and precision

The inter day precision and accuracy of rivaroxaban in human plasma were determined atLLOQ, low, medium, and high QC sample concentrations. Six replicates at each QC sample concentration level were assayed at different days total of3 precision and accuracy batches. Intraday precision and accuracy for rivaroxaban in human plasma were determined at LLOQ,low, medium and high QC sample concentrations. A total of six replicates at each QC sample concentration level were assayed within a single batch. The intraday and interday precision was expressed as % CV, the obtained results were less than 15% for all QC concentrations. The accuracy was expressed as a percentage of nominal values, obtained results are within ±15% for all the QC concentrations, the results were given in Table 1.

Matrix factor

Matrix factor was calculated at low and high QC concentrations for each of the eight independent matrix lots including lipemic and haemolysed plasma. Two neat solutions containing both analyte and internal standard, whose concentrations are equivalent to those of the processed low QC and high QC respectively (assuming 100% recovery). These solutions are used to reconstitute various extracted blank matrices during matrix factor testing. In addition to this, these neat solutions are injected directly as comparison samples for the matrix factor test. The % CV of matrix factors for all blank types, was within acceptance criteria of 15%. No significant matrix effect was observed at low and high concentration level. The results were presented in Table 2.

Recovery

The recovery was calculated by comparing the peak area of analyte and IS in plasma samples with the peak area responses of six replicates of pure solutions representing 100% extraction yield. The evaluation was assessed at low (1.408 ng/mL), medium (217.262 ng/mL) and high (482.803ng/mL) QC concentrations. The overall average recovery of rivaroxaban and IS were found to be 69.7 and 74.3 % respectively. The results were presented in Table 3.

Stability studies

The stability of rivaroxabanin plasma were assessed under different conditions like bench top, freeze thaw cycle, auto sampler, post preparative, blood stability and long term stability. The bench-top stability was established for 7 hours at wet ice bath, four repeated freeze–thaw cycles was established at -20°C, the auto sampler stability was established for 46 hours at 10°C, post preparative stability was established for 52 hours at 2-8°C and long-term stability was evaluated for 71 days at -20°C. The mean percentage nominal values of the analytes for all the stability tests carried out were found to be within ±15% of the predicted concentrations at their LQC and HQC levels. Stock solutions of rivaroxaban and rivaroxaban D4 were found to be stable for 20 days at 2-8°C. The results were presented in Table 4.

CONCLUSION

A rapid, simple, selective, precise and accurate LC-MS/MS method was developed and validated for the quantification of rivaroxaban in human K_2EDTA plasma with a limit of quantitation of 0.5 ng/mL. The method was proved to be accurate, precise and robust during the method validation. The method was shown to be adequate and reliable for application to pharmacokinetics and bioequivalence studies of rivaroxaban tablets.

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Table 1: Interday and intraday run accuracy and precision

Interday				Intraday		
Spiked Blood concentration (ng/mL)	**Concentration obtained (ng/mL)**	**Precision (%)**	**Accuracy (%)**	**Concentration obtained (ng/mL)**	**Precision (%)**	**Accuracy (%)**
0.518 (LLOQ)	0.555	4.1	107.2	0.562	3.9	108.4
1.394 (LQC)	1.464	2.4	105.0	1.482	1.8	106.3
215.086 (MQC)	215.680	1.3	100.3	215.671	1.3	100.3
467.579(HQC)	457.600	1.1	97.9	459.123	0.9	98.2

Table 2. Matrix Factor

	Matrix factor at low level (LOQ)			Matrix factor at High level (HQC)		
Sample No.	**MF-Analyte**	**MF-Internal standard**	**IS Normalized MF**	**MF-Analyte**	**MF-Internal standard**	**IS Normalized MF**
1	98.3	98.1	100.2	95.2	93.9	101.4
2	98.3	98.2	100.1	96.4	94.8	101.8
3	97.3	94.9	102.6	95.1	94.0	101.2
4	95.9	94.9	101.1	95.7	96.5	99.1
5	93.4	95.9	97.4	96.6	95.5	101.1
6	98.3	95.9	102.5	95.3	95.7	99.5
7	91.8	94.4	97.3	95.2	94.7	100.6
8	93.8	95.9	97.8	94.3	95.1	99.2
Mean	**95.9**	**96.0**	**99.9**	**95.5**	**95.0**	**100.5**
%CV	**2.7**	**1.5**	**2.2**	**0.8**	**1.0**	**1.1**

Table 3: Percent Recovery of Rivaroxaban and Rivaroxaban D4 in human plasma

Rivaroxaban		Rivaroxaban **D4**	
Concentration (ng/mL)	Recovery %	Concentration (ng/mL)	Recovery %
1.394 (LQC)	67.9	1200.02	74.3
215.086 (MQC)	71.0		
467.579 (HQC)	70.1		
Mean Recovery	**69.7**		

Table 4: Stability data for Rivaroxaban under different conditions

Stability	Storage condition	Level	% stability
Bench top stability	Wet ice (7 hours)	LQC	99.7
		HQC	96.2
Auto sampler stability	At 10 °C (46 hours)	LQC	95.6
		HQC	91.8
Post preparative stability	2-8°C (52 hours)	LQC	95.5
		HQC	92.9
Freeze Thaw stability	After 4 cycle (-20 °C)	LQC	99.8
		HQC	96.3
Long term stability in Blood	at -20 °C (71 days)	LQC	106.3
		HQC	98.27
Short term stock solution stability	Room temperature (17 hours)	Analyte	101.0
		IS	103.4
Long term stock solution stability	at 2-8°C (20 days)	Analyte	96.7
		IS	102.2

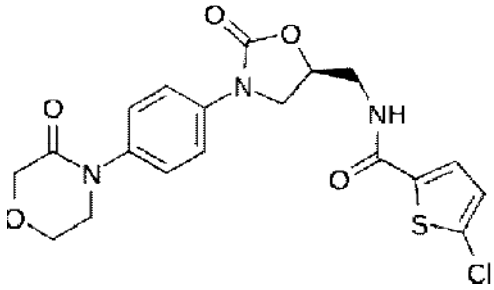

Figure 1: Chemical structure of Rivaroxaban

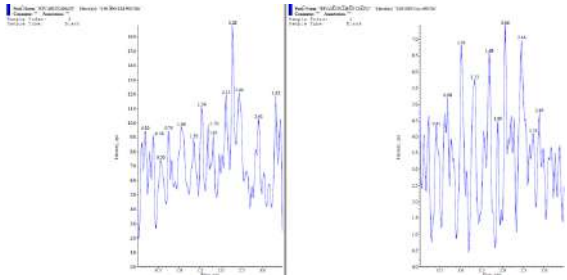

Figure 2: Chromatogram of blank human plasma

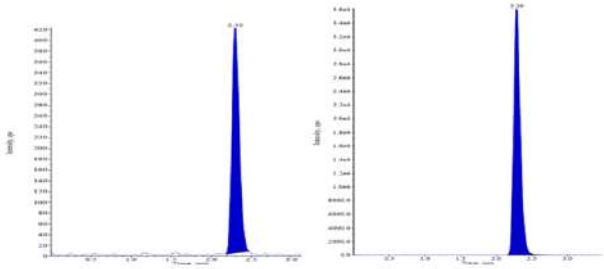

Figure 3: LLOQ chromatogram of Rivaroxaban and Rivaroxaban D4

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RESEARCH ARTICLE

Study of Tensile Properties of Glass and Kevlar Reinforced Composites

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ABSTRACT

The field of glass polymers has brought about a quantum growth in its basic as well as technological aspects. The review of work presented here reveals that bulk of the effort has gone into the understanding of the mechanical properties of composites. A thorough literature search reveals that there are no systematic studies mechanical properties of composites. There is ample scope for fabrication of newer composites with constant weight fractions of glass fiber in polymers and their characterization for mechanical properties. In this project, a wealth of data on mechanical properties of glass fiber composites has been generated. These data are useful for material technologists and mechanical engineers, who can make use of this data base for the generation of new materials for specific applications. In this work the hybrid polymer composite is prepared by reinforcing glass and kevlar fibers with polystyrene resin and using Matched-die moulding method of fabrication and An experiment tensile test is carried out as per ISO-527/ASTMD638 standard to calculate the Young's modulus of the material.

Keywords: Hybrid Composite, Composite Fabrication, Matched-die moulding, ISO-527/ASTMD638.

INTRODUCTION

The development of composite materials and their design and production technologies is one of the vital advances in the history of materials. Composites are used in various fields having their unique mechanical and physical properties and are developed for particular application. Composite materials having a vital advantages over other materials such as tensile strength, impact strength, flexural strengths, stiffness and fatigue characteristics. Due to

their numerous advantages they are widely used in the various research and commercial industries .A composite material is a load-bearing material (called reinforcement) that is combined with a weaker material (called a matrix)..The primary functions of the matrix are to transfer stresses between the reinforcing fibers/particles and to protect them from mechanical properties. Due to their distinctive properties. In general, fibers are the most important aggregates in composites because they meet the desired conditions and impart strength to the substrate, influencing and enhancing the desired properties. A fiber is characterized by its length being much greater as compared to its cross-sectional dimensions. The properties of matrix, fiber and its interface have greatly influencing the properties of composite materials. Fibers in polymer composites can either synthetic/man-made fibers or natural fibers. Some commonly used synthetic fibers for composites are glass, kevlar and carbon etc. There are many types of glass fiber depending upon the type of application like E-glass fiber (electrical application), C-glass (corrosive environment), S-glass (structural application, high temperature). Glass fibers are available in various forms such as continuous, chopped and woven fabrics etc. Among all reinforcing fibers, natural fibers have gained great significance as reinforcements in polymer matrix composites. Depending upon the source of origin, natural fibers are classified as plant, animal and mineral fibers. Due to the global energy crisis, natural fibers reinforced polymer composites have attracted more research interests. The main advantages of natural fibers are their availability, biodegradable, renewable, environmental friendly, low cost, low density, high specific properties, good thermal properties and enhanced the energy recovery, low energy consumption, non-abrasive nature and low cost.

Scope of the Present Investigation

A probe by accident into the field of glass polymers has brought about a quantum growth in its basic as well as technological aspects. The synthetic organic polymers with the combinational properties of existing conventional high strength polymers, glass fiber's have altogether offered a new field of research. The review of work presented here reveals that bulk of the effort has gone into the understanding of the mechanical properties of composites. A thorough literature search reveals that there are no systematic studies mechanical properties of composites. There is ample scope for fabrication of newer composites with constant weight fractions of glass fiber in polymers and their characterization for mechanical properties. In this project, a wealth of data on mechanical properties of glass fiber composites has been generated. These data are useful for material technologists and mechanical engineers, who can make use of this data base for the generation of new materials for specific applications.

Background to the Present Problem

The foregoing discussion indicates that the bulk of the investigations on composites are confined mostly to the improvements in properties of material like glass and Kevlar fiber. Large number of investigators has conducted experiments to establish the mechanical properties of these composites. Further, it is observed effort is seen to characterize completely a composite material from the point of view of using polymers compositions. Any composites must be investigated from the view point of mechanical properties and its breakdown strength if it is to be used in such applications. Composites provide flexibility to modify the parameters mentioned above by changing the composition of the materials themselves. Such modification needs to be investigated.

Objectives of This Study

The main objectives of this study are the modification and development of new series of polymeric materials for different applications like automobiles, aerospace and characterization of the developed materials. Influence of fabrication, composition, and mechanical behavior of the composites has been closely investigated.

The Present Problem

The focus of this investigation is to develop new series of polymer composites and perform their characterization using physic-mechanical. Suitability for applications in new technological areas by experimentation is an important task of this investigation. Considering the gap areas, the present need and the ongoing technological interests, a closed look has been taken at the composites from the point of application as well flexibility in arriving at the

required specifications. The possibility of arriving at interesting composite applications such as variable automobiles, aerospace etc have been examined and reported.

Preparing a Composite

Most composites are made up of just two materials. One material (matrix or binder) surrounds and binds together a cluster of fibers or fragments of a much stronger material (the reinforcement). In fiberglass, the reinforcement is provided by fine threads or fibers of glass, often woven into a sort of cloth and the matrix is a plastic.

The threads of glass in fiber glass are very strong under tension but they are also brittle and will snap if bent sharply. The matrix not only holds the fibers together, it also protects them from damage by sharing any stress among them. The matrix is soft enough to be shaped with tools, and can be softened by suitable solvents to allow repairs to be made. Any deformation of a sheet of fiberglass necessarily stretches some of the glass fibers, and they are able to resist this, so even a thin sheet is very strong. It is also quite light, which is an advantage in many applications.

Over recent decades many new composites have been developed, some with very valuable properties. By carefully choosing the

- **Matrix**
- **Reinforcement,** and
- **Manufacturing process** that brings them together,

The materials used to achieve this work are :

- **Glass fiber** of 1.27 SQM
- **Kevlar fiber** of 1.23 SQM
- **Epoxy resin** and **hardener**

Glass Fiber Chemical Composition

Chemical composition variation within a glass type is form differences in available glass batch raw materials, or in the melting and forming process, or from different environmental constraints at the manufacturing site. These compositional fluctuations do not significantly alter the physical or chemical properties of glass type. Very tight control is maintained within a given production facility to achieve consistency in the glass composition for production capability and their weight ranges for four type of commercial glass fibers.

Kevlar Fiber

Fiber Properties: They are characterized by medium to ultra-high strength, medium to low elongation and moderately high to ultra-high modulus with the densities ranging from 1.38g/cm3 to 1.47g/cm3. Heat-resistant and flame-resistant kevlar fibers contain high proportion or meta-oriented phenylene rings, whereas ultra-high strength high-modulus fibers contain mainly para oriented phenylene rings.

Mechanical Properties: Kevlar yarn has a breaking tenacity of 3045 MPa, in other words more than 5 times than this of steel (under water, kevlar is 4 times stronger) and twice than this of glass fiber or nylon. High strength is a result of its aromatic and amide group and high crystallinity. Kevlar retains strength and modulus at temperatures as high as 300 degrees Celsius. It behaves elastically under tension

Epoxy Resin

Lapox L12 is a liquid, unmodified epoxy resin of medium viscosity which can be used with various hardeners for making glass fiber reinforced composites. The choice of hardener depends on the processing method to be used and on the properties required of the cured composite. Hardener K6 is low viscosity room temperature curing liquid hardener. It is commonly employed for hand layup and for other fabrication methods. Being rather reactive, it gives a short pot life and rapid cure at normal ambient temperatures. Laminates can be subjected to operating temperatures of 100^0 C.

Specifictions of Resins and Hardeners

Lapox L-12

Epoxide equivalent	gm/eq	182 - 192
Epoxy value	eq/kg	5.2 - 5.5
Viscosity at 25^{0}C	mpa.s	9000 -12000

Hardener K-6

Visual appearance		Pale Yellow liquid
Refractive index at 25^{0}C		1.4940 – 1.5000
Water content		1% max
Shear strength on A1 alloy lap joint		1.4 Kgmm^2 min

Processing parameters

Lapox L-12		100 pbw
Hardener K-6		10 – 12 pbw
Viscosity at 20^{0}C	mPa/s	5,000 – 8,000
Pot life at 20^{0}C	hrs	0.5 – 1

Lapox L-12 and Hardener K-6 can be mixed easily at room temperature.When using the prepreg technique, the impregnated cloth is passed through the heating zone of a conveyor oven where it is procured. For 15 mins at 100^{0}C (Or) For 03 mins at 150 C.The prepreg thus obtained will be dry to touch.

Curing

25^{0}C	14 – 24 hrs
80^{0}C	01 – 02 hrs
100^{0}C	15 – 30 mins
140^{0}C	05 – 10 mins

Production of FRP's

Matched-die moulding method is carried out for fabrication of fibers.

Matched Die Moulding

This is a common method of composite manufacturing using performs. The compound is laid between a male and female die called the matched die, and mechanically pressed to obtain the required shape. In addition, heat is applied depending up on the cure requirements. Since, the component is pressed between two mould surfaces, both the surfaces of the part will have fine surface finish and dimensional control is good.

Based on the resin properties the composite is cured for 15-30 minutes, operated at 100^{0}C.

Tensile Test

Tensile tests measure the force required to break a specimen and the extent to which the specimen stretches or elongates to that breaking point. Tensile stress produces a stress-strain diagram, which is used to determine tensile modulus. The data is often used to specify a material, to design parts to withstand application force and as a quality control check of material. Since the physical properties of many materials can vary depending on ambient temperature, it is sometimes appropriate to test materials at temperatures that simulate the intended end use environment.

Equipment

- Instron universal tester
- Extensometer

Specimen Size

The most common specimen for ASTM D638 is a type 1 tensile bar. The most common specimen for ISO527 is the ISO3167 type 1A multipurpose specimen. ASTM D882 uses strips cut from thin sheet or film.

Test procedure

Specimens are placed in the grips of the instron at a specified grip separation and pulled until failure. For ASTM D638 the test speed is determined by the material specification. For ISO 527 the test speed is typically 5 or 50mm/min for measuring strength and elongation and 1mm/min for measuring modulus. An extensometer is used to determine elongation and tensile modulus.

Data

The fallowing calculation can be made from tensile test results;

- Tensile strength (at yield and at break)
- Tensile modulus
- Strain
- Elongation and percent elongation at yield
- Elongation and percent elongation at break

Tensile Test Results

Tensile test result of composite specimens of glass fiber and kevlar

Tensile Behavior of Glass and Kevlar Polymer Composite

Ten specimens from each fiber orientation of the composite were tested. The dimensions of the test coupons were 170 mm in length,10 mm in width, and, 2.75 mm in thickness respectively. The 10 sample specimens were tested at a speed of 5 mm / min.

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Table (1) Standard specification of glass fiber

	Unit		**Tolerance specification**
Wave pattern		plain	DIN ISO 9354
Area weight	g/m²	202	+/-5% DIN EN 12127
Yarn	tex		DIN EN 12654
Warp Weft		EC9 68 EC9 68	
Fiber count	1/cm		DIN EN 1049
Warp ends Weft picks		17.2 +/- 5% 12.0 +/- 5%	
Tensile strength	N/cm		DIN EN 12654
Warp Weft		500 350	
Finish content	%	0.10 – 0.30	DIN ISO 1887
Thickness (approx)	mm	0.18	DIN ISO 4603/E
Temperature resistance	°c		
Continuous load Short time resistance		260 300	

Table (2) Standard Specification of Kevlar Fiber

Fiber material	100% KEVLAR	
Weave pattern	PLAIN	ISO 2711/1
Weight [g/m²]/[oz/sq.yd]	195+/-5	ISO 3801
Tensile strength at break	7700/8200	EN ISO 13934-1
Max.elongation at break	3.5/3.9	EN ISO 13934-1
Circular bend test(N)	15.2	ASTM D 4032
Modulus(GPa) warp/weft	67.6/67.6	ASTM D 885
Thickness [um]	400	ISO 5084
Moisture content (%)	2.7	
Finish	NONE	

Table (3) Tensile test results

SPECIMEN	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
PEAK LOAD (Kg)	763.8	661.5	693.5	640.2	779.4	727.6	744.6	809.9	825.2	730.9
BREAK LOAD	1.8	3.6	2.6	2.2	2.7	2.7	2.4	2.1	1.8	0.8

(Kg)										
ELONGATION AT PEAK LOAD(mm)	5.24	4.79	5.06	4.91	5.55	5.58	5.48	5.63	5.63	5.23
TENSILE AT PEAK LOAD (N/sq.mm)	272.46	235.97	247.39	228.37	278.03	259.55	265.6	286.41	294.37	260.73
TENSILE AT BREAK LOAD (N/sq.mm)	0.642	1.284	0.927	0.785	0.963	0.963	0.856	0.861	0.92	0.285
ULTIMATE MODULUS (Mpa)	12384.6	12731.1	11691.3	11691.7	13034.2	12773.1	13792.1	22127.7	12731.1	12297.9
SECANT MODULUS (Mpa)	1.078	1.078	1.078	1.078	1.078	1.078	1.078	1.078	1.078	1.078

Table (4)Young's modulus of glass and Kevlar polymer specimens

Specimen	Young's modulus in N/ mm²
1	4160
2	3938.4
3	3911.5
4	3721.2
5	4007.9
6	3775.6
7	3877.9
8	4070.1
9	4183.2
10	3988.5
AVERAGE	3963.43

Figure (1) Glass fiber

Figure (2) Kevlar fiber

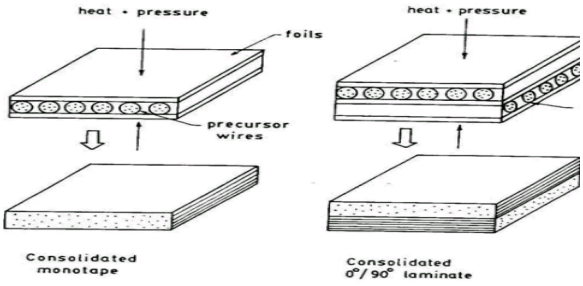
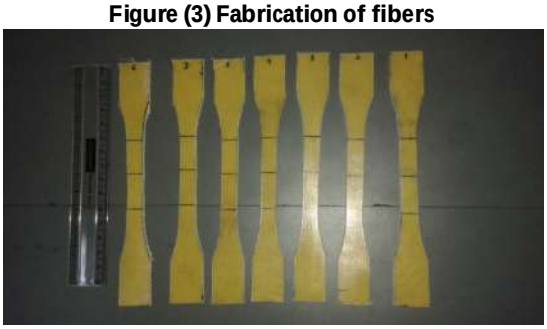
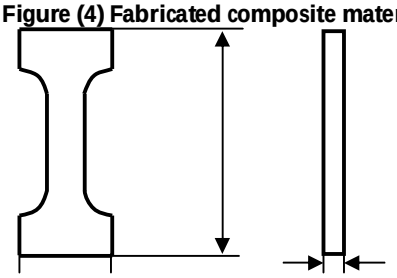


Figure (3) Fabrication of fibers

Figure (4) Fabricated composite material





Specimen dimensions Length-170mm
Breadth-20mm Thickness -3mm

Figure (5) Specimens for tensile test

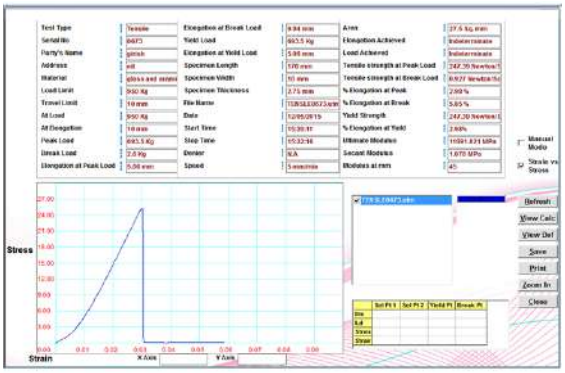


Figure (6) Stress v/s strain curve of specimen

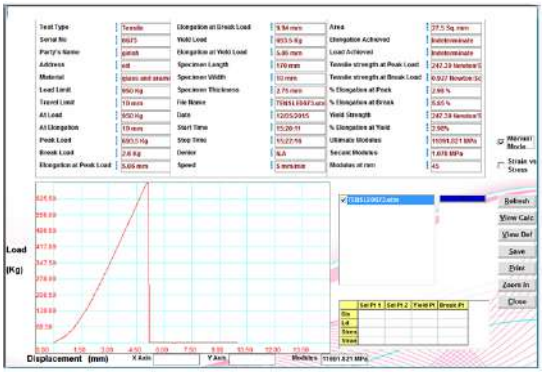


Figure (7) Load v/s displacement curve of specimen

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REVIEW ARTICLE

A Review on Documentation in Pharmaceutical Industry

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ABSTRACT

Method of making ready a written material , which describes the manner in time period of specifications, coaching etc. The D & C Act beneathneath situations of granting license and schedule M require producer of drug to preserve diverse records. There are diverse kinds of approaches that a GMP facility follows. Given underneath is a listing of the common types of files. A record or set of files specifying the beginning fabric with their portions and the packaging substances, collectively With an outline of the method and precautions required to provide a designated amount of a completed product in addition to the processing commands, which include the in-technique controls." A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that can be used to offer exclusive targeted records approximately facilities, operation, or articles used in the mass produce, purifying, packaging, and storing of one or greater human drugs. Construction Sites, Facilities, Operating Procedures and Personnel Drug material, Drug material Intermediates, and Ingredients Used in their composition, or Drug result. Packaging Material. Excipients, colourants, flavours, essences, or ingredients used in their preparation. FDA Accepted Reference Information. Each DMF have to include most effective one form of statistics and all helping facts. See Section IV.C of the rule of thumb for extra targeted descriptions of the sort of statistics favored in every type. Supporting statistics and facts in a DMF may be go referenced to another DMF. A generic drug is a pharmaceutical drug this is equal to a brand-call product in dosage, strength, path of administration, quality, performance, and supposed use, however does now no longer bring the brand call. This phase offers the important thing statistics for gaining approval of an ANDA. Bioavailability is the charge and volume of drug to be had on the web website online of motion. The first-class sections indexed under include very much the equal statistics as might be submitted in a NDA.

Keywords : Food and Drug Administration (FDA), . Excipients, colourants.

INTRODUCTION

Method of making ready a written material, which describes the manner in time period of specifications, coaching etc. The D & C Act beneathneath situations of granting license and schedule M require producer of drug to preserve diverse records. Documentation is vitala part of the fine guarantee machine and as such, must be related to all factor of GMP. Its goal is to outline the specs for all substances and the technique of manufacture and control, to make certain that each one employees worried with manufacture have the information vital to determine whether or not or now no longer to launch a batch of a drug for sale, and to provide an audit patha good way to allow research of the records of any suspected defective batch. The specs must describe in element the requirement with which the goods or materials used or acquired throughout manufacture should conform. They function a foundation for quality evaluation. Documentation provides the route for audit or stases the overall quality of operations inside a company and the very last product.

IMPORTANCE OF DOCUMENTATION [3]

- Provide vital operating details,
- Reduces the hazard of mistake,
- Helps in reducing batch to batch variation,
- Considered as records of batch operations.

TYPES OF DOCUMENT [4,5,6,7]

There are diverse kinds of approaches that a GMP facility follows. Given underneath is a listing of the common types of files.

1. **Quality manual:** A international business enterprise record that describes, in paragraph form, the rules and /or elements of the rules that the business enterprise is needed to follow.
2. **Policies:** Documents that describe in popular terms, and now no longer with step-through-step commands, how unique GMP aspects (inclusive of security, documentation, health, and responsibilities) might be implemented.
3. **Standard running approaches (SOPS):** Step-through-step commands for appearing operational responsibilities or activities.
4. **Batch statistics:** These files are generally used and finished through the producing branch. Batch statistics offer step-through-step commands for production-associated responsibilities and activities, except together with regions at the batch document itself for documenting such responsibilities.
5. **Test techniques:** These files are generally used and finished through the fine control (QC) branch. Test techniques offer step-through-step commands for trying out supplies, materials, products, and different production-associated responsibilities and activities, e.g., environmental tracking of the GMP facility. Test techniques generally include paperwork that ought to be crammed in on the give up of the procedure; that is for documenting the trying out and the outcomes of the trying out.
6. **Specifications:** Documents that listing the necessities that a supply, material, or product ought to meet earlier than being launched to be used or sale. The QC branch will examine their take a look at outcomes to specs to decide in the event that they byskip the take a look at.
7. **Logbooks:** Bound series of paperwork used to record activities. Typically logbooks are used for documenting the operation, maintenance, and calibration of apiece of equipment. Logbooks also are used to document crucial activities, e.g.; tracking of smooth rooms, answer preparation, recording of deviation, extrade controls and its corrective motion assignment.

MASTER FORMULA RECORD [8,9,10,11]

Definition: A record or set of files specifying the beginning fabric with their portions and the packaging substances, collectively With an outline of the method and precautions required to provide a designated amount of a completed product in addition to the processing commands, which include the in-technique controls."
Master manufacturing commands need to consist of:

The name of the intermediate/AP/ method being synthetic and an figuring out record reference code, if applicable. A entire listing of uncooked substances and intermediates (precise via way of means of names or code497sufficiently precise to perceive any unique first-class characteristic). An correct assertion of the amount or ratio of every uncooked fabric or intermediate for use, which include the unit of measure. Where the amount isn't fixed, The calculation for every batch length or price of manufacturing need to be covered. Variations to portions need to be covered anywhere justified. The manufacturing vicinity and important manufacturing device for use.

Detailed manufacturing commands, which include the:

- Sequences to be accompanied
- Ranges Of technique parameters for use
- The methods, or connection with the methods, for use for making ready the essential device (e.g., cleaning, assembling)
- Sampling commands and in-technique controls, with their recognition standards in which suitable deadlines for final touch of character processing steps and/or the entire technique, in which suitable
- Expected yield levels at suitable stages of processing or time in which suitable, unique notations and precautions to be accompanied, or Cross references to these Instructions for garage of the intermediate or API/semi-completed formulations to guarantee its suitability for use; commands need to cowl the labeling (specimen label sand packaging substances and uniquegarage situations with deadlines, in which suitable).

Master Formula Record is like wise referred to as MFR, Master Production Record. MFR is used as reference widespread for making ready batch production report (BMR) via way of means of production units. It is ready via way of means of the studies and improvement crew of the company. It includes all Information approximately the producing technique for the product. Master Formula Record (MFN) is a grasp record for any pharmaceutical product. MFR performs an important. Inconsistency for every batch production. There will be Master Formula facts referring to all production techniques for every product and batch length to be synthetic. These will be organized and recommended via way of means of the ready technical body of workers i.e., head of manufacturing and first-class control. A Master Formula Record is ether organizedprimarily based totally upon enjoy of impotent certified body of workers like production chemist or analytical chemist or organized primarily based totally upon batch production report of a batch length.

MFR includes :[12,13,14]

- **Product Details :** Name, brand and cope with of the producing company Dosage shape call. Brand call, Generic call. Product code and Label declare of all ingredients
- **Product description :** Batch length, Pack length and packing style Shelf existence and Storage situations
- **MFR variety and date:** Supersede MFR variety and date Effective batch variety Authorization via way of means of the manufacturing and first-class guarantee head
- **Equipment:** A listing of all required device and machines required within side the Manufacturing technique with their capacity
- **Special commands:** The precautions and unique commands to be accompanied for the duration of the product production and packing
- **Calculations:** Include the calculation steps of all lively substances to get the 100% of the lively fabric. The calculation is carried out the use of water or LOD to get 100% potency

- **Manufacturing Process:** All steps in all levels of the producing technique are written. All manner pace like shifting, milling, lubricating, granulation, compression and coating are write down in element which insert the technique time and yield. It additionally consist of atmospheric situations as temperature, humidity, and garage situations for each step
- **Packing Process:** List of all packing substances with their amount is written. Line clearance, reconciliation of revealed and unprinted packing substances need to be covered in details
- **Yield:** Include the theoretical, real yield and recognition restriction of the batch. Primary Responsibility is of FD and Production Department and secondary obligation is of Quality Assurance Department. Accountability lies with Head-Quality Assurance for Implementation of SOP.

DRUG MASTER FILES

INTRODUCTION [15,16]

A Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that can be used to offer exclusive targeted records approximately facilities, operation, or articles used in the mass produce, purifying, packaging, and storing of one or greater human drugs. The submission of a DMF isn't required through regulation or FDA regulation. A DMF is submitted entirely on the discretion of the holder. The evidence carrys in the DMF can be used to help an Investigational New Drug Application (IND), a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), any other DMF, an transport Application, or amendments and dietary additive to any of these.

A DMF is NOT an alternative choice to an IND, NDA, ANDA, or Export Application. It isn't authorised or disapproved. practical please of a DMF are reviewed most essential in reference to the outline of an IND, NDA, ANDA, or an Export Application. This guiding principle does now no longer impose obligatory requirements . It does, however, provide steering on perfect strategies to assembly regulatory requirements. Different strategies can be followed, however the applicant is advocated to speak about tremendous versions earlier with FDA reviewers to prevent spending effort and time in making ready a submission that FDA can also additionally later decide to be unacceptable. Drug Master Files are supplied for in 21 CFR 314.420. This guiding principle is supposed to offer DMF holders with techniques perfect to the enterprise for making ready and filing a DMF. The guiding principle discusses forms of DMF's, the records wished in every type, the layout of submissions to a DMF, the executive techniques governing overview of DMF's, and the responsibilities of the DMF holder. When an applicant references its very own cloth, the applicant need to reference the records contained in its very own IND, NDA, or ANDA without delay as opposed to setting up a brand new DMF.

DEFINITIONS[17,18,19]

For the functions of this guiding principle, the subsequent definitions apply:

1. Agency way the Food and Drug Administration.
2. Agent or consultant way any man or woman who's appointed through a DMF holder to function the touch for the holder.
3. Applicant way any man or woman who submits an software or abbreviated software or an modification or complement to them to acquire FDA approval of a brand new drug or an antibiotic drug and every other man or woman who owns an authorised software .
4. Drug substance way an lively component this is supposed to grant pharmacological interest or different direct impact withinside the diagnosis, cure, mitigation, treatment, or prevention of ailment or to have an effect on the shape or any feature of the human body, however does now no longer consist of intermediates used withinside the synthesis of such component .
5. Export software way an software submitted below segment 802 of the Federal Food, Drug, and Cosmetic Act to export a drug that isn't authorised for advertising and marketing withinside the United States.
6. Holder way someone who owns a DMF.

7. Letter of authorization way a written announcement through the holder or targeted agent or consultant allowing FDA to consult records withinside the DMF in assist of any other man or woman's submission.
8. Person consists of character, partnership, corporation, and affiliation. (Section 201(e) of the Federal F, D, & C Act.)
9. Sponsor way someone who takes duty for and initiates a scientific investigation. The sponsor can be an character or pharmaceutical company, governmental enterprise, educational institution, personal organization, or different organization.

TYPES OF DRUG MASTER FILES[20,21,22,23,24]

There are five types of DMF's:

Type I - Construction Sites, Facilities, Operating Procedures and Personnel

Type II - Drug material, Drug material Intermediates, and Ingredients Used in their composition, or Drug result

Type III - Packaging Material

Type IV - Excipients, colourants, flavours, essences, or ingredients used in their preparation

Type V - FDA Accepted Reference Information

Each DMF have to include most effective one form of statistics and all helping facts. See Section IV.C of the rule of thumb for extra targeted descriptions of the sort of statistics favored in every type. Supporting statistics and facts in a DMF may be go referenced to another DMF (see Part V).

Type I: construction Site, Facilities, Operating Procedures, and Personnel

A Type I DMF is usually recommended for someone outdoor of america to help FDA in engaging in on web website online inspections in their production facilities. The DMF have to describe the producing web website online, device capabilities, and operational layout. A Type I DMF is commonly now no longer had to describe home facilities, besides in unique cases, including while someone isn't always registered and now no longer mechanically inspected. The description of the web website online have to consist of acreage, real web website online address, and a map displaying its area with admire to the closest city. An aerial photo and a diagram of the web website online can be beneficial. A diagram of important manufacturing and processing regions is beneficial for information the operational layout. Major device have to be defined in phrases of capabilities, application, and area. Make and version could now no longer commonly be wished except the device is new or unique. A diagram of important company organizational elements, with key production, great control, and great guarantee positions highlighted, at each the producing web website online and company headquarters, is likewise beneficial.

Type II - Drug material, Drug material Intermediates, and Ingredients Used in their composition, or Drug result

Type II DMF should overall be banned as an unmixed drug intermediate, drug substance, drug product, or material used for his or her preparation. Drug Intermediates, Drug Substances, and Materials Used in Their Preparation Summarize all the major steps within the production and control of a pharmaceutical intermediate or substance. Guidelines for the submission of supporting documents in pharmaceutical applications for the manufacture of pharmaceutical substances.

Guidelines for the layout and content material of the chemistry, production and manipulate segment of an application.

Drug product

If this statistics can not be provided in an IND, NDA, ANDA, or export application, it have to be submitted to the DMF. Guidelines for the layout and content material of the chemistry, creation and manage phase of an application. Guidelines for submission of files for the manufacture and manage of pharmaceutical products. Guidelines for filing samples and analytical statistics for technique validation

Type III: Packaging Material

Each packaging fabric have to be recognized with the aid of using the meant use, additives, composition, and controls for its launch. The names of the providers or fabricators of the additives utilized in getting ready the

packaging fabric and the attractiveness specs have to additionally be given. Data helping the acceptability of the packaging fabric for its meant use have to additionally be submitted as mentioned with inside the "Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics." Toxicological facts on those substances could be covered below this form of DMF, if now no longer in any other case to be had with the aid of using go connection with some other document.

Type IV - Excipients, colourants, flavours, essences, or ingredients used in their preparation

Each additive have to be recognized and characterised with the aid of using its technique of manufacture, launch specs, and trying out methods. Toxicological facts on those substances could be covered below this form of DMF, if now no longer in any other case to be had with the aid of using go connection with some other document. Usually, the reputable compendia and FDA rules for colour additives (21 CFR Parts 70 thru 82), direct meals additives (21 CFR Parts one hundred seventy thru 173), oblique meals additives (21 CFR Parts 174 thru 178), and meals materials (21 CFR Parts 181 thru 186) can be used as reassets for launch tests, specs, and safety. Guidelines counseled for a Type II DMF can be beneficial for getting ready a Type IV DMF. The DMF have to consist of another helping statistics and facts that aren't to be had with the aid of using go connection with some other document.

Type V: FDA Accepted Reference Information

FDA discourages the usage of Type V DMF's for miscellaneous statistics, replica statistics, or statistics that have to be covered in one of the different kinds of DMF's. If any holder needs to publish statistics and helping facts in a DMF that isn't always included with the aid of using Types I thru IV, a holder have to first publish a letter of reason to the Drug Master File Staff (for address, see D.5.a. of this section). FDA will then touch the holder to speak about the proposed submission.

GENERIC PRODUCTS [25,26,27,28,29]

A generic drug is a pharmaceutical drug this is equal to a brand-call product in dosage, strength, path of administration, quality, performance, and supposed use, however does now no longer bring the brand call. A generic drug ought to include the identical energetic substances because the unique emblem-call formulation. The FDA calls for that generic tablets undergo a rigorous evaluation technique to acquire approval. The FDA guarantees a generic medicine offers the identical scientific advantage and is as secure and powerful because the brand-call remedy that it duplicates. In maximum cases, everyday merchandise emerge as to be had after the patent protections afforded to a drug's unique developer expire.

Generic drugs generally tend to price much less than their brand-call opposite numbers due to the fact they do now no longer must repeat animal and scientific (human) research that have been required of the brand-call drugs (throughout submitting in their NDAs) to illustrate protection and effectiveness. According to the Hatch–Waxman Act, ordinary drugs only need to demonstrate bioequivalence to an already authorized brand-name drug to get FDA approval. Bioequivalence approach that the energetic element in the generic drug is absorbed on the identical fee because the brand-call drug. The take a look at required to illustrate bioequivalence is a lot much less high priced than the ones undertaken via way of means of brand-call tablets. This provision in Hatch–Waxman has allowed generics to go into the market place fast and at a lot decrease price. For example, earlier than Hatch–Waxman in 1983, most effective 35% of top-promoting tablets with expired patents confronted generic opposition. By 1998, that quantity become near 100% (Higgins & Rodriguez, 2006).

When more than one generic organizations marketplace the identical product, marketplace opposition generally consequences in fees approximately 85% much less than the brand call (Generic Drug Facts, 2018). As in line with the statistics supplied via way of means of Association for Accessible Medicines, generics account for 89% of prescriptions disbursed in the United States, however most effective 26% of the full drug costs (AAM, 2018).

FDA's Orange Book carries statistics on each innovator producer's patents for his or her merchandise which might be submitted for approval. These normally consist of patents for element, composition, or use (however now no longer

technique). Generic producer sought to seek advice from this post edlisting earlier than they could determine whether or not to mission any patent. If they determine to mission a patent, they ought to notify the FDA, in addition to the innovator producer and patent holder. Typically, the patent holder will eventually carry a patent infringement in shape towards the generic producer, inside forty five days of receipt of note of a mission to its patent. The FDA ought to then withhold approval of the generic product for a duration of 30 months. Some pharmaceutical patents may be prolonged to get better time misplaced in the regulatory approval technique, as described via way of means of the patent time period recovery below the Hatch–Waxman Amendments (Zannou, Li, & Tong, 2009, pp. 911–921). For the primary generic corporation to mission a patent indexed for an innovator drug, one marketplace exclusivity provision of the 1984 Amendments offers a 180-day head begin to the marketplace. To marketplace a generic drug inside United States, a corporation ought to record an Abbreviated New Drug Application (ANDA) below segment 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) with the FDA. Once authorised, an applicant can also additionally manufacture and marketplace the generic drug product to offer a secure, powerful, low price opportunity to the American public. An essential degree of ANDA technique is the approval of the "first generics." As the call suggests, first generics are the primary approval via way of means of FDA which lets in a producer to marketplace a generic drug product in United States. FDA considers first generics to be essential to public fitness and prioritizes evaluation of those submissions.

A key metrics for the pharmaceutical enterprise is the quantity of novel tablets and primary generics approved inside a given 12 months from 2013 to 2017, the quantity of novel tablets approved ranged from 22 to 46. In the identical duration, general quantity of first generics approved ranged from seventy three to 106. This indicates the tempo of novel tablets improvement is a lot slower than the tempo of generics improvement, because of the good sized quantity of scientific trials that novel drug producer sought to do to set up protection and efficacy. Another essential enterprise standards that might be monitored is that of ways fast a unique drug may be made to be had into a primary everyday. A image of that is supplied in which it could take everywhere from 6 to 30+ years for a unique drug to be made to be had into a primary generic.

The cause for this big variance may be attributed to patent protections round a unique drug, issue in setting up the protection and efficacy of a generic while in comparison with the radical drug, or every other full-size technical information that maintains the generic opposition at bay.

ABBREVIATED NEW DRUG APPLICATION (ANDA)[30,31]

The Abbreviated New Drug Application (ANDA) is supplied for the advertising and marketing of generic drug merchandise in any case varieties of exclusivity have expired for the ¬reference-indexed drug (innovator drug). ANDAs are filed below the FD&C Act segment 505(j).1 The numbers of ANDAs submitted to the FDA has been growing gradually on the grounds that 2001 probable because of the excessive call for for decrease price generic merchandise than brand merchandise, and extra organizations getting into the manufacture of generic merchandise. Generic drug merchandise ought to be bioequivalent to the innovator product, though waivers of in vivo bioequivalence observe are available in sure cases.23 The energetic pharmaceutical element, dosage form, dose strength, labeling, path of administration, and situations ought to be similar to the reference indexed drug (RLD). Also, a generic drug product ought to meet the identical specs because the RLD, if the RLD is indexed in the USP, and meet the identical cGMP necessities for production because the RLD. A sponsor of an ANDA ought to record a patent certification with the FDA. Table 37.7 indicates the distinction in the statistics required for the submission of an ANDA, as opposed to a NDA.

Formation and pacify of an Abbreviated New Drug Application (ANDA) [32,33]

The FDA strongly recommends that an ANDA be submitted in the CTD format, both paper or electronic.24 The necessities from CFR, and the corresponding sections in the CTD for ANDAs, are summarized . More statistics at the ANDA checklist for CTD or e-CTD may be discovered from the FDA website.

Basis for an ANDA Submission.

Patent Certification and Exclusivity Statement
Sponsors of an ANDA ought to document a patent certification below one of the following paragraphs:
That no patent statistics at the drug product this is the concern of the ANDA has been submitted to the FDA;
That such patent(s) has expired;

The time on such patent runout; or that such patent is invalid sale use of the pharmaceutical product from which the ANDA is submitted. The above are generally referred as Paragraphs I, II, III or IV Certifications. If the ANDA applicant documents the Paragraph IV certification, the applicant ought to additionally notify the innovator inside 20 days of submitting of an ANDA, and the innovator has 45 days to take action upon receiving the notification. The FDA may also keep the approval as much as 30 months, relying at the final results of the litigation, If there is any comparison between the generic medicine and the reference listed medicine. This phase must examine the lively ingredients, in addition to the path of administration, dosage form, and electricity of the drug products.

LABELING[34]

According to 21CFR314.94(8), variations among the applicant's proposed labeling, and labeling accredited for the reference indexed drug, may also consist of variations in expiration date, formulation, bioavailability or pharmacokinetics, labeling revisions made to conform with present day FDA labeling suggestions or different steering or omission of an illustration or different factor of labeling included with the aid of using patent or accorded exclusivity under phase 505 (j)(4)(D) of the act. All labeling for a frequent drug product ought to be supplied in SPL formatting, and in compliance with the Physician's Labeling Rule (PLR).

BIOAVAILABILITY/BIOEQUIVALENCE [35, 36]

This phase offers the important thing statistics for gaining approval of an ANDA. Bioavailability is the charge and volume of drug to be had on the web website online of motion. Bioequivalence is the absence of a considerable distinction in the charge and volume of drug to be had on the website online of motion after dosing of a check product, as compared to a reference product. In general, bioequivalence is evaluated with the aid of using evaluating the bioavailability of the check, and the reference products, in crossover medical research on healthful subjects. The examine may also consist of the assessment of bioavailability of products administered with, and without, food. Recommendations of examine designs and information assessment for bioequivalence examine are indexed in regulatory steering.26,27 Bioequivalence is carried out while the 90% self belief interval (CI) for the ratio of Cmax and AUC of the check product over the reference product on log converted information is inside 80%–125%.

CMC Information [37, 38 ,39, 40]

The first-class sections indexed under include very much the equal statistics as might be submitted in a NDA. The content material of the CMC for an ANDA consists of the following:
Components and composition statements;
Raw substances;
Description of producing facility;
Outside firms;
Agreement checking out laboratories;
Manufacturing and processing instructions;
In-method statistics;
Packaging substances controls;
Controls for the completed dosage form;
Analytical methods;
Stability of completed dosage form;
Samples;
Environmental considerations;
Other; Sterilization guarantee information and data.

To modernize the CMC evaluation for technological know-how and risk-primarily based totally pharmaceutical exceptional evaluation of ANDA applications, the FDA has evolved and applied a question-primarily based totally evaluation (QbR) approach, this consists of a demand for the sponsor to put up a exceptional ordinary summary (QoS). To facilitate the QbR, the FDA has developed version exceptional ordinary summaries for immediate-release (IR) or extended-release (ER) stable oral dosage forms.

CONCLUSION

Pharmaceutical manufacture and law is definitely an worldwide business. With the growing emphasis on harmonization efforts and well known setting, in addition to mutual popularity agreements, expertise of overseas policies is a have to each for expertise the destiny course of those efforts in addition to for world wide deliver of drug products. It is expected that the technique defined right here could be a beneficial reference paintings for the ones employees making ready and the use offices for pharmaceutical manufacture. It can function a device for schooling team of workers and can show to be beneficial for first-rate warranty experts for evaluation of compliance throughout self-inspection. It is once more emphasized that documentation is a totally critical issue of GMP and could decorate the visibility of the first-rate warranty function.

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RESEARCH ARTICLE

Efficacy of Foliar Application of Plant Activators on Sesame Leaf Spot Incidence of Rice

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ABSTRACT

The present studies were undertaken to investigate the effect of foliar application of resistance inducing chemicals or plant activators against brown spot in rice. A field experiment was conducted during Navarai season at Puthoor Village using ADT 36 (susceptible) as test cultivar. All the eight resistance inducing chemicals at their maximum inhibitory conc. identified from the screening pot trials were sprayed individually at disease initiation stage and repeated once at fifteen days interval. The untreated plots served as control. The results revealed that, acetyl salicylic acid @ 200 ppm reduced the brown spot disease incidence as against in control. It was followed by methyl salicylic acid @ 100 ppm which was statically at par. Also, the data indicated that the disease was minimum in plots sprayed thrice with methyl salicylic acid at 15, 30 and 45 DAT followed by plots receiving two sprays at 15 and 30 DAT which were statistically at par.

Keywords: rice, brown spot, resistance inducing chemical, acetyl salicylic acid, methyl salicylic acid.

INTRODUCTION

Rice continues to be the major staple food crop for human population. With the twin forces of population growth and economic expansion particularly in Asia, world rice requirements are expected to increase by 1.7 per cent annually between 1990 and 2025. Although seemingly small, this growth rate translates into an additional requirement of 13 million tonnes of rice per year. With less land available to expand rice-growing areas with competing demands from urbanization and industrialization on existing rice lands and irrigation water, production increases should come from intensive agriculture in existing lands of favourable and less favourable areas. This can yield some negative non target effects such as serious increases in pest and disease pressure, for instance the

catastrophe caused by rice brown spot. The brown spot of rice or *Helminthosporium* leaf spot or Helminthosporiosis or sesame leaf spot or seedling blight caused by *Bipolaris oryzae* is the most widely occurring disease and at times attains dreadful proportions. The fungus *B.oryzae* causes characteristic leaf spot on all the susceptible varieties. The pathogen is capable of infecting the rice plant at all stages of its growth. On susceptible varieties the spots are much larger and may reach one cm or more in length. Sometimes numerous spots occur and as a result the leaf withers. Also, concentric lines or zones on the spot have been observed occasionally. The disease also causes the major Bengal famine during 1942-43. Spots are formed on the blade and sheath of the leaf (Ou, 1985). The resistance phenomenon against blast is attributed to many factors among which resistance inducing chemicals play a major role. Reports are also in hand indicating induction of resistance in rice plants to *Rhizoctonia solani* by using non-conventional chemicals, which are known as inducers of phytoalexins and or elicitors of resistance in different plant species (Dantre *et al.,* 2003). The present studies were undertaken to investigate the effect of foliar application of resistance inducing chemicals or plant activators against brown spot in rice.

MATERIALS AND METHODS

Crop, Variety and Source

Crop : Paddy (*Oryza sativa* L.)
Variety : ADT 36
Source : Tamilnadu Rice Research Institute (TRRI), Aduthurai, Tamilnadu

The disease incidence was assessed by adopting 0-9 scale according to "Phytopathometry" by Mayee and Datar (1986) and the per cent disease incidence /index was calculated based on the formula suggested by Vidhyasekaran *et al.* (1989).

DISEASE SEVERITY	DESCRIPTION OF DISEASE INDEX
0	No lesions
1	Affected leaf area less than 1 %
3	1-10 % affected leaf area
5	11-25 % affected leaf area
7	26 -50 % affected leaf area
9	> 50 % leaf area affected

$$\textbf{Per cent Disease Index} = \frac{\text{Total ratings}}{\text{Total number of leaves graded} \times \text{Maximum grade in the score chart.}} \times 100$$

Field experiment

Separate field studies were conducted to test the efficacy of certain resistance inducing chemicals (At their respective MIC's) for assessing their influence on the incidence of brown spot of rice. The brown spot susceptible variety ADT 36 was used for the study. The experiments were conducted in a randomized block design with three replications for each treatment and a suitable control. Also, the fertilizer application was done following the blanket schedule of 120:38:38 of N: P: K recommended by the State Agricultural department. A plot size of 5X4 m was maintained for each treatment and the crop was raised with the spacing of 12.5 X 10 cm and all the standard agronomic practices as recommended by the State Agricultural Department were followed. The fungicide carbendazim 50 WP @ 0.1 per cent was used for comparison. The rice crop was harvested at maturity, thrashed, winnowed and cleaned plot wise, dried and the yields of grain and straw were recorded. In all the screening field trials the observations on disease incidence was assessed on a randomly selected set of 25 hills per plot at the time of maturity. Also, the grain and straw yield of rice was recorded and expressed as t/ha.

Evaluation of resistance inducing chemicals against brown spot of rice

A field experiment was conducted during December, 2019 - March, 2020 at Puthoor Village using ADT 36 (susceptible) as test cultivar. All the seven resistance inducing chemicals at their maximum inhibitory conc. identified from the screening pot trials were sprayed individually at disease initiation stage and repeated once at fifteen days interval. The untreated plots served as control.

Sl.No.	Resistance inducing chemicals	Concentration
1.	Cupric chloride (CC)	100 ppm
2.	Methyl salicylic acid	100 ppm
3.	Acetyl Salicylic acid	200 ppm
4.	K_2HPO_4	1000 ppm
5.	Acibenzolar S- Methyl	200 ppm
6.	NAA	1000 ppm
7.	INA	100 ppm

Effect of spraying Acetyl salicylic acid (@200 ppm) at different crop growth stages on brown spot incidence and yield of rice var. ADT 36

The most effective spray timing of acetyl salicylic acid (ASA) (200 ppm) was ascertained by spraying it once, twice and thrice at different crop growth stages (15, 30 and 45 DAT) in a pot culture experiment conducted using ADT 36 (susceptible) as test cultivar.

RESULTS AND DISCUSSION

Effect of foliar application of certain resistance inducing chemicals on brown leaf spot incidence of rice var. ADT 36 (Field experiment)

The most effective conc. of resistance inducing chemicals were tested against brown spot and the results are presented in table 1. The results revealed that, acetyl salicylic acid @ 200 ppm reduced the brown spot disease incidence by 14.41 per cent as against 38.72 per cent in the control. It was followed by Methyl salicylic acid @ 100 ppm (14.58%) which was statically at par. The treatment with NAA (24.92%) was the least effective one. Among the various resistance inducing chemicals, acetyl Salicylic acid recorded 5.16 t/ha of grain yield and 7.18 t/ha of straw yield.

Effect of spraying ASA (200 ppm) at different crop growth stages on brown spot incidence and grain yield of paddy

The data indicated that the disease incidence (18.12 %) was minimum in plots sprayed thrice with acetyl salicylic acid at 15, 30 and 45 DAT followed by plots receiving two sprays at 15 and 30 DAT (18.40 %) which were statistically at par (Table 2). The grain yield and straw yield were also higher in plots sprayed thrice with acetyl salicylic acid (15, 30 and 45 DAT) followed by plots receiving two sprays at 15 and 30 DAT. Among the various treatments the plots receiving single spray (T_3) was the least effective. The control plots recorded 38.78 per cent disease incidence, 3.98 t/ha of grain yield and 5.84 t/ha of straw yield. Reports are available on the effectiveness of naturally occurring and synthetic chemical compounds as abiotic inducers of resistance in susceptible plants. Studies have shown that SAR is induced in several plant species by treatment with chemicals such as salicylic acid, methyl-2,6-dichloroisonicotinic acid (INA) or benzo(1,2,3)thiadiazole-7-carbothionic acid *S*-methyl ester (BTH) (Hammerschmidt *et al.,* 2001).

Acibenzolar-S-methyl (enzo(1,2,3) thiadiazole-7-carbothioic acid S-methyl ester), referred to as ASM, is a synthetic molecule from Novartis whose role as a plant defence activator has been demonstrated in a number of crops including *Arabidopsis* (Lawton *et al.,* 1996), tobacco (Friedrich *et al.,* 1996), wheat (Gorlach *et al.,* 1996), bean (Siegrist *et al.,* 1997), maize (Morris *et al.,* 1998), barley (Beber *et al.,* 2000), sunflower (Sauerborn *et al.,* 2002), tobacco (Perez *et al.,*

2003), amaranthus (Nair *et al.,* 2007), pepper (Baysal *et al.,* 2005), apple (Bengtsson *et al.,* 2008) and cucumber (Narusaka *et al.,* 1999). ASM is one of the most potent disease resistance activators used in crops to control pathogens including viruses (Sindela rova *et al.,* 2002), bacteria (Oh *et al.,* 2004) and fungi (Achuo *et al.,* 2004). This compound was further developed by Syngenta (Kessmann *et al.,* 1996) and introduced in 1996 as a 'plant activator' to control wheat powdery mildew in Germany and Switzerland (Ruess *et al.,* 1996). It is commercially released in some countries as a plant health promoter of annual crops under the name of Bion or Actigard (Brisset *et al.,* 2000). Veronesi *et al.* (2009) mentioned that foliar spray and soil drenching of ASM and potassium phosphonate reduced the incidence of broom rape (*Orobanche ramose* L.) in oilseed rape (*Brassica napus* L.). Also, the bio-compatible products Actigard (acibenzolar-S-methyl), disodium hydrogen phosphate and alum (aluminium potassium sulphate) also suppressed Mungbean Yellow Mosaic Virus (MYMV) on black gram (Venkatesan *et al.,* 2010). The induction of resistance with ASM was accompanied by a significant increase in peroxidases and polyphenoloxidases activities in sugar cane (Ramesh sundar *et al.,* 2006).

Salicylic acid (SA) is a plant-derived compound induced resistance against pathogens and stimulated plant growth (Nickell, 1983). It was also reported that SA plays an important role in plant defense by the development of SAR against pathogens (Ryals *et al.,* 1994). SA has been shown to be a signalling molecule involved in both local defence reactions at infection sites and the induction of systemic resistance (Durner *et al*., 1997). SA is a phenolic compound present in many plants and is an important component in the signal transduction pathway involved in local and systemic resistance to pathogens (Frey and Carver, 1998). The findings of Percival *et al.* (2009) lends support to the present observations on the use of Salicylic acid (SA) derivatives who proved that salicylic acid sprayed at different growth stages in apple and pear increased the resistance against scab. The use of SA at low conc. is taken up more easily into crop plants than higher conc. Sometimes, higher conc. of SA treated plants are killed (Frey and Carver, 1998). In the present study also Acetyl Salicylic Acid was found very effective at 200 ppm conc. and cost wise also cheaper. In this respect, chemicals like acetyl salicylic acid may especially be suitably used as inducers of disease resistance.

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Table 1 Effect of foliar application of certain resistance inducing chemicals on brown leaf spot incidence of Rice var. ADT 36 (Field experiment)

T. No.	Chemicals	Dose	Disease incidence (%)	Grain yield (t/ha)	Straw yield (t/ha)
1.	Cupric chloride	100 ppm	24.36	4.35	6.49
2.	Methyl Salicylic acid	100 ppm	14.58	5.08	7.12
3.	Acetyl Salicylic acid	200 ppm	14.41	5.16	7.18
4.	K_2HPO_4	1000 ppm	21.64	4.46	7.03
5.	Acibenzolar S- Methyl	200 ppm	19.98	4.58	6.27
6.	NAA	1000 ppm	24.92	4.19	6.44
7.	INA	100 ppm	22.60	4.61	6.59
8.	Carbendazim	0.1 %	16.83	4.72	6.56
9.	Control		38.72	3.69	5.43
10.	C.D. (p=0.05)		4.17	0.31	0.40

Table 2. Effect of spraying Acetyl Salicylic Acid (@200 ppm) at different crop growth stages on brown spot incidence *and grain yield of rice var. ADT 36 (Pot culture)*

T. No	Treatments	*Stages of spraying*	Disease incidence (%)	Grain yield (t/ha)	Straw yield (t/ha)
1	T_1	15 DAT	19.43	4.99	6.99
2	T_2	30 DAT	19.80	4.61	6.80
3	T_3	45 DAT	23.18	4.33	6.39
4	T_4	$T_1 + T_2$	18.40	4.97	7.02
5	T_5	$T_1 + T_3$	20.14	4.69	6.91
6	T_6	$T_2 + T_3$	21.28	4.60	6.79
7	T_7	$T_1 + T_2 + T_3$	18.12	5.05	7.09
8	T_8	Carbendazim	14.63	4.39	6.43
9	T_9	Control	38.78	3.98	5.84
		C.D. (p=0.05)	5.31	0.09	0.23

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RESEARCH ARTICLE

The GC MS Study of One Ayurvedic Formulation, 'Punarnavasavam

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ABSTRACT

In order to known the molecules present in one Ayurvedic medicine, Pipplayasavam, it was subjected to GC MS analysis. This medicine is prescribed for ailments such asbowel diseases, anaemia, piles, cough, intestinal gas and abdominal distension, loss of appetite, anorexia. The medicine was procured from standard Ayurvedic vendor at Chennai and was processed as per protocol before GC MS analysis. The GC MS profile indicated the presence of some medicinally important molecules such as Eugenol, Undecanoic acid, 10-methyl-, methyl ester, Methyl tetradecanoate, Hexadecanoic acid, methyl ester, 12, 15-Octadecadienoic acid, methyl ester, Methyl stearate, n-Propyl 9,12-octadecadienoate, Oleic Acid, Octadecanoic acid, 17-methyl-, methyl ester, Squalene, i-Propyl 5,8,11,14,17-eicosapentaenoate, .beta.-Sitosterol etc. which could directly or indirectly contribute to the action of Pipplyasavam. It is concluded

that there could be some direct or indirect role of the molecules present in Pipplyasavam in curing digestive disorders.

Keywords: Pipplyasavam, GC MS, Ayurvedic,anaemia, anorexia, Eugenol, Squalene.

INTRODUCTION

Ayurvedic and other forms of complementary and alternative medicinal practices are in vogue since time immemorial. The need to standardize these medicines in the light of modern medical practices is immensely required. The present study is one more attempt in this regard by these workers who have embarked upon establishing the efficacy of Ayurvedic medicines and other complementary and alternative medicines. [1-29]This work reports the GC MS analysis results of one Ayurvedic medicine, Pippalyasavam, which is prescribed for the treatment of bowel diseases, anaemia, piles, cough, intestinal gas, and abdominal distension, loss of appetite, anorexia, and fevers. It acts on the stomach and increases the secretion of gastric juices. It also acts on the liver and stimulates bile secretion into the intestine. Thus, it improves appetite and digestion. It is also detoxifying in its action, which reduces the formation and accumulation of Aama (toxins) in the body. It is best for people having Kapha and Vata dominance in their symptoms.

Ingredients: one part each of Pippali– *Piper longum*, Kali Mirch – *Piper nigrum*, Chavya – *Piper chaba*, Turmeric (*Curcuma longa*), Chitrak – *Plumbago zeylanica*, Nagarmotha – *Cyperus rotundus*, Vaividanga – *Embelia ribes*, Supari – *Areca catechu*, Lodhra – *Symplocos racemosa*, Patha – *Cissampelos pareira*, Amla (*Phyllanthus embelica*), Ushira – *Vetiveria zizanioides*, SafedChandan – *Santalum album*, Kushta – *Saussurea lappa*, Laung – *Syzygium aromaticum,* Tagara (*Valleriana wallichi*), Jatamansi (*Nardostachys jatamansi*), Dalchini – *Cinnamomum zeylanicum*, Cardamom (*Elletaria cardamomum*), Indian bay leaves (*Cinnamomom tamala*), Priyangu – *Callicarpa macrophylla* (flowers) and Nagakesara(*Mesuaferrea***)** are mixed with 1024 parts of water, 600 parts of Jaggery, 20 parts of Dhataki (*Woodfordica fruticosa*) flowers, and 120 parts of grapes (*Vitis vinifera*) and kept tightly packed in asava/arishat vessel for one month. After that the fluid is filtered as bottled as medicine. 10 to 30 ml of Pippalyasavam is taken with equal amount of water twice a day after food or as prescribed by the physician. The reference for this medicine is from Sarnagadhar Samhita Madhyama Khanda 28 to 33.

MATERIALS AND METHODS

Pippalyasavam was obtained from standard Ayurvedic vendor at Chennai and was subjected to GC MS analysis by standard procedure. The compounds are identified by GC-MS Library (NIST & WILEY).

RESULTS AND DISCUSSION

The GC MS profile of Pippalyasavam is represented in Figure 1. Table1 indicates the retentions time, types of possible compound, their molecular formulae, molecular mass, percentage peak area and their medicinal roles of each compound as shown in the GC MS profile of Pippalyasavam. The identification of metabolites was accomplished by comparison of retention time and fragmentation pattern with mass spectra in the NIST spectral library stored in the computer software (version 1.10 beta, Shimadzu) of the GC-MS along with the possible pharmaceutical roles of each bio molecule as per Dr. Duke's Phytochemical and ethnobotanical data base (National Agriculture Library, USA) and others as shown in Table 1 [30]. Table 1 indicates the presence of important biomolecules such as Eugenol, Undecanoic acid, 10-methyl-, methyl ester, Methyl tetradecanoate, Hexadecanoic acid, methyl ester, 12, 15-Octadecadienoic acid, methyl ester, Methyl stearate, n-Propyl 9,12-octadecadienoate, Oleic Acid,

Octadecanoic acid, 17-methyl-, methyl ester, Squalene, i-Propyl 5,8,11,14,17-eicosapentaenoate, .beta.-Sitosterol etc. which have multiple roles that could support the medicinal role of Pipplayasavam.

CONCLUSION

The presence of medicinally important molecules could assist in the function of Pippalasavam towards curing gastric ailments. It will be of interest to understand the medicinal roles of those molecules which are not known.

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Table1. Indicates the retentions time, types of possible compound, their molecular formulae, molecular mass, percentage peak area and their medicinal roles of each compound as shown in the GC MS profile of Pippalyasavam

Sl. No	Retention Time	Compound Name	Mol. Formula	Mol. Weight	% Peak Area	Possible medical Role
1	6.225	3-Phenylpropanol	C9H12O	136.1	3.22	Not known
2	6.526	Coumarin, 3,4-dihydro-4,4,7-trimethyl-	C12H14O2	190.1	1.39	Not known
3	7.1	5-(Hydroxymethyl)-2-(dimethoxymethyl)furan	C8H12O4	172.1	23.21	Not known
4	7.84	Eugenol	C10H12O2	164.1	7.21	Eugenol has many medicinal properties such as antifungal, antioxidant, anticonvulsant, local anaesthetic, anti-stress, bacteriostatic, bactericidal, anti-carcinogenic, depresses activity of central nervous system, anti-radiation, antiviral, induces apoptosis in melanoma cells and HL-60 leukemia cells.[31-32]
5	8.59	Benzene, 1,1'-(1-methylethylidene)bis[4-methoxy-	C17H20O2	256.1	1.24	Not known
6	9.771	Phenol, 3,5-bis(1,1-dimethylethyl)-	C14H22O	206.2	0.85	Not known
7	9.955	Undecanoic acid, 10-methyl-, methyl ester	C13H26O2	214.2	1.43	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
8	10.396	Estra-1,3,5(10)-trien-17.beta.-ol	C18H24O	256.2	1.28	Not known
9	12.18	Methyl tetradecanoate	C15H30O2	242.2	1.38	Catechol-O-Methyl-Transferase-Inhibitor, Methyltransferase-Inhibitor, Methyl-Donor, Methyl-Guanidine-Inhibitor
10	14.211	Hexadecanoic acid, methyl ester	C17H34O2	270.3	5.02	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor,

						Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
11	15.739	12,15-Octadecadienoic acid, methyl ester	C19H34O2	294.3	2.54	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
12	15.807	11-Octadecenoic acid, methyl ester	C19H36O2	296.3	8.37	Catechol-O-methyl-Transferase Inhibitor, methyl donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
13	16.069	Methyl stearate	C19H38O2	298.3	2.21	Catechol-O-methyl-Transferase Inhibitor, methyl donar, Methyl Guanidine Inhibitor
14	16.335	n-Propyl 9,12-octadecadienoate	C21H38O2	322.3	6.18	Anaphylactic, Antitumor, Arylamine-N-Acetyltransferase-Inhibitor. Decreases Norepinephrine Production, Down regulates nuclear and cytosol androgen reuptake, GABA-nergic, Increases Natural Killer (NK) Cell Activity, Inhibits Production of Tumor Necrosis FactorAntitumor, anticancer, myoneuro-stimulant, decreases norepinephrine production, NADH-Oxidase inhibitor, NADH-Ubiquinone Oxidoreductase inhibitor
15	16.399	Ethyl Oleate	C20H38O2	310.3	5.90	Not known
16	16.462	Oleic Acid	C18H34O2	282.3	0.75	Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity

17	16.664	Octadecanoic acid, 17-methyl-, methyl ester	C20H40O2	312.3	0.91	Catechol-O-methyl-Transferase Inhibitor, methyl donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
18	18.32	7-Methyl-Z-tetradecen-1-ol acetate	C17H32O2	268.2	0.81	Oligosaccharide provider
19	18.801	Octasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13,15,15-hexadecamethyl-	C16H50O7Si8	578.2	1.19	Not known
20	19.412	Bis(2-ethylhexyl) phthalate	C24H38O4	390.3	2.14	Not known
21	20.625	Octadecane, 3-ethyl-5-(2-ethylbutyl)-	C26H54	366.4	0.89	Not known
22	20.96	Heptasiloxane, hexadecamethyl-	C16H48O6Si7	532.2	10.60	Not known
23	21.472	Squalene	C30H50	410.4	7.04	Monooxygenase inhibitor, biochemical precursor ofsteroid synthesis, natural moisturizer, used in cosmetics
24	22.011	Octatriacontylpentafluoropropionate	C41H77F5O2	696.6	1.11	Not known
25	22.434	Geranylisovalerate	C15H26O2	238.2	0.80	Not known
26	22.473	Octadecanoic acid, 4-hydroxy-, methyl ester	C19H38O3	314.3	0.74	17 beta hydroxysteroid dehydrogenase inhibitor, Aryl hydrocarbon hydroxylase inhibitor, testosterone hydroxylase inducer, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
27	23.145	i-Propyl 5,8,11,14,17-eicosapentaenoate	C23H36O2	344.3	0.75	Ionotrpoic, 11B-HSD inhibitor, 5 alpha reductase inhibitor, HIF1 alpha inhibitor, Alpha amylase inhibitor, IkappaB-alpha alpha phosphorylation inhibitor, Interlukine- 1 alpha inhibitor, Testosterone 5 alpha reductase inhibitor, 12 Lypoxygease inhibitor, 17 beta hydroxysteroid

						dehydrogenase inhibitor, 5 HETE inhibitor, 5 HT inhibitor, 8 HETE inhibitor, ACE inhibitor, Acetyl CoA carboxylase inhibitor
28	24.375	.beta.-Sitosterol	C29H50O	414.4	0.85	17 beta hydroxysteroid dehydrogenase inhibitor, Antiamyloid beta, Anti TGF beta, Beta receptor agonist, Beta-adrenergic receptor blocker, beta blocker, beta galactosidase inhibitor, beta glucuronidase inhibitor, ER beta binder

Qualitative Compound Report

Data File	200520019.D	**Sample Name**	Pippalyasavam
Sample Type		**Position**	20
Acq Method	GC Screening Method.M	**Acquired Time**	22-05-2020 AM 08:14:38
Comment			

User Chromatogram

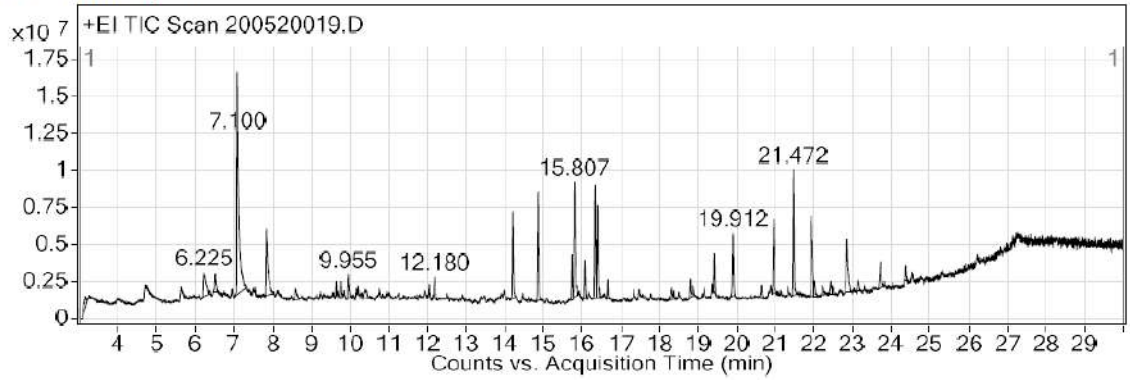

Figure 1. Depicts the GC MS profile of Pipplayasavam

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REVIEW ARTICLE

A Review on Vaccines

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ABSTRACT

Vaccine is a biological substance that is introduced into the body to prevent infection or to control disease due to certain pathogen which is disease causing organism such as a virus, bacteria or parasite. Vaccines are usually administered by needle injections (parenteral administration), and but some are given orally or even nasally (in the case of flu vaccine).A vaccine is inducing the body immune system and produce the antibodies action against the disease-causing microorganism. vaccinations can also prevent widespread of diseases in populations and therefore the side effect of vaccinations.

Keywords: Vaccine, Disease, Immunity, Antigen, Pathogen.

INTRODUCTION

Vaccine is a biological substance that is introduced into the body to prevent infection or to control disease due to certain pathogen like virus, bacteria or parasite. Vaccines are usually administered by needle injections, but some are given orally or nasally. A vaccine can confer active immunity against a specific harmful agent by stimulating the immune system to attack the agent. Vaccines protect against many diseases. Examples include tetanus, diphtheria, mumps, measles, pertussis (whooping cough), meningitis, and polio. Many of these infections can cause serious or life-threatening illnesses and may lead to life-long health problems. Because of vaccines, many of these illnesses are now rare. The administration of vaccines is named vaccination. Vaccination is that the best method of preventing infectious diseases. Vaccination is that the most successful medical approach to disease prevention and control. In the future, vaccines have the potential to be used not only against infectious diseases but also for cancer as a preventive and treatment tool.

Aim and Objectives

The main aim of the present work is to review on recent advancement of vaccines and the possible modification for the future development of vaccines.

Objectives

1. Rapidly increase the immunization coverage.
2. Reduction of pressure on the health care system.
3. To save lives, prevent premature death and disability
4. Reduce health sector costs for hospital care.
5. Disease elimination.

Types of Vaccine [2]

- There are several different types of vaccines. Vaccines may be viral (live or inactivated), viral vector, subunit (protein or polysaccharide) or nucleic acid (DNA or RNA). Combination vaccines may include inactivated, protein-basedor protein-conjugated polysaccharide vaccine components.
- There has been an increased focus on vaccine development using the viral-vector and nucleic-acid based platforms since the appearance of the SARS-CoV-2 virus and COVID-19 disease in late 2019.

1. live Attenuated
2. Inactivated
3. Toxoid
4. Subunit
5. Conjugate
6. Heterotypic
7. Viral vector
8. Nucleic acid-based vaccines

Live Attenuated Vaccine [3]

- Live attenuated vaccines contain whole bacteria or viruseshave been "weakened" (attenuated).so, it can replicate in the body several times and generate an immune response without causing the disease,because these vaccines are similar to the natural infection that they help prevent, they create a strong and long-lasting immune response. Just 1 or 2 doses of most live vaccines can give you a lifetime of protection against a germ and the disease it causes.
- When the vaccine virus is given to a person, it'll be unable to cause illness, but will still provoke an immune reaction which will protect against future infection. e.g., The BCG vaccine contains live weakened tuberculosis bacteria.

Killed or Inactivated Vaccines [4-5-6]

- Inactivated vaccines contain whole bacteria or viruses have been killed.so, they cannot replicate. However, theydo not always create such a strong or long-lasting immune response as live attenuated vaccines. inactivated vaccines are prepared by using heat or chemicals like formaldehyde or formalin.
- This destroys the pathogen's ability to duplicate, but keeps it "intact" in order that the system can still recognize it.

Toxoids [7-8]

- Immunizations for this type of pathogen are often made by inactivating the toxin that causes disease symptoms. like organisms or viruses utilized in killed or inactivated vaccines, this may be done via treatment with a chemical like formalin, or by using heat or other methods.
- Immunizations created using inactivated toxins are called toxoids. Toxoids can actually be considered killed or inactivated vaccines, but are sometimes given their own category that they contain an inactivated toxin, and not an inactivated form of bacteria.

Subunit and Conjugate [9]

- The vaccines contain proteins or sugars derived from the disease-causing organisms. Both subunit and conjugate vaccines contain only pieces of the pathogens they protect against.
- Subunit vaccines use only part of a target pathogen to provoke a response from the immune system. This may be done by isolating a specific protein from a pathogen and presenting it as an antigen on its own. e.g., The acellular pertussis vaccine and influenza vaccine are examples of subunit vaccines.

Conjugate [10]

- Conjugate vaccines are designed from parts of the bacterial coat. However, these parts won't produce an efficient immune response when presented alone. Hence, they're combined with a carrier protein. These carrier proteins are chemically linked to the bacterialcoat derivatives. They generate a stronger response and may protect the body against future infections. e.g., Vaccines against pneumococcal bacteria used in children

Viral Vector [11-12]

- Viral vector-based vaccines differ from most conventional vaccines therein they don't actually contain antigens, but rather use the body's own cells to supply them. By infecting cells and instructing them to make large amounts of antigen, which then trigger an immune response, the vaccine mimics what happens during natural infection with certain pathogens - especially viruses. e.g., of a viral vector vaccine is the rVSV-ZEBOV vaccine against Ebola
- There are two main sorts of viral vector-based vaccines. Non-replicating vector vaccines are unable to form new viral particles; they only produce the vaccine antigen. Replicating vector vaccines also produce new viral particles within the cells they infect, which then continue to infect new cells which will also make the vaccine antigen.

Nucleic Acid-Based Vaccines [13]

- At present, different types of nucleic-acid vaccines are in developmental, pre-clinical and clinical evaluation phases, e.g., for prevention of human immunodeficiency virus (HIV), influenza and malaria diseases and treat some cancers.
- Nucleic acid vaccines use genetic material from a disease-causing virus or bacterium to stimulate an immune response against it.
- Depending on the vaccine, the genetic material could be DNA or RNA; in both cases it provides the instructions for making a specific protein from the pathogen.
- Nucleic acid vaccines work in a different way to other vaccines in that they do not supply the protein antigen to the body. Instead, they provide the genetic instructions of the antigen to cells in the body and in turn the cells produce the antigen, which stimulates an immune response. Nucleic acid vaccines are quick and easy to develop.

Vaccines Discovered

1796-Cowpox Vaccine

Small pox is acute contagious viral disease. It was contagious means, it spread from one person to another. it was a serious infectious disease caused by the variola virus.

Symptoms of Small pox.

1. Fever
2. Overall discomfort.
3. Headache
4. Severe fatigue
5. Severe back pain
6. Vomiting

Diagnosis [14-15]

1. Febrile prodrome occurring 1 to 4 days before rash onset.
2. Fever ≥101°F (38.3°C).
3. Smallpox can be diagnosed based on the patient's clinical signs and symptoms.
4. The disease can be definitively diagnosed by isolation of the virus from the blood or lesions,

- Dr. Edward Jenner collected bits of cowpox pustule the animal variant of smallpox and scratched it into the arm of an 8-year-old boy.
- Cowpox is a disease caused by the cowpox virus. The virus is transferable between species, like from cat to human. The transferral of the disease was first observed in dairymaids who touched the udders of infected cows and consequently developed the signature pustules on their hands.
- Cowpox is commonly found in animals. the highly contagious and sometimes deadly smallpox disease.The cowpox vaccinations proved so successful,that in 1980.Once vaccinated, a patient develops antibodies that make them resistant to cowpox, but they also develop immunity to the variola virus, or smallpox virus.
- Smallpox affected all levels of society. In the 18th century in Europe, 400,000 people died annually of smallpox. The case-fatality rate varied from 20% to 60%.The case-fatality rate in infants was even higher, approaching 80% in London and 98% in Berlin during the late 1800s.

1881-Anthrax Vaccine [16]

Anthrax is an infectious disease caused by a gram-positive rod-shaped bacterium called Bacillus anthracis. Anthrax is a bacterial disease of sheep and cattle that can also be transmitted to humans.

Symptoms

1. Fever
2. Swelling of the neck
3. Sore throat.
4. Pain when swallowing.
5. Nausea, vomiting and vomiting blood.
6. Diarrhoea or bloody diarrhoea.
7. Headache.

Diagnosis [17]

- Biopsy (tissue sample)
- Blood test
- Chest x-ray or computed tomography (CT)
- French biologist Louis Pasteur has successfully developed an anthrax vaccine. Pasteur exposed the anthrax pathogens to heat and oxygen to weaken them, but not to kill them.
- The human anthrax vaccine was developed by the Soviet Union in the late 1930s and the United States and the United Kingdom in the 1950s. The current vaccine approved by the U.S. Food and Drug Administration (FDA) was developed in the 1960s.
- All vaccines currently in use have been shown to cause serious reactions and adverse events in approximately 1% of recipients. There are not more than 2,000 cases per year.
- If treated, cutaneous anthrax is rarely fatal because the infected area is limited to the skin. Without treatment, approximately 20% of skin infections will progress to death.
- Before 2001, the death rate from pulmonary anthrax was 90%; since then, they need to drop to 45%. Gastrointestinal infections are usually treated, but they usually end with a mortality rate of 25% to 60%, depending on when treatment starts. This type of anthrax is the rarest.

1885-Rabies Vaccine[18]

- Rabies is a viral infection that is spread mainly through the bite of an infected animal.

- Rabies virus causes rabies. If left untreated, it is usually fatal. Viruses can affect the body in two ways: directly entering the peripheral nervous system (PNS) and traveling to the brain. The virus is spread via the saliva of an infected animal. Rabies, also known as hydrophobia. The virus multiplies rapidly in the brain. This activity can cause severe inflammation of the brain and spinal cord, after which people will quickly deteriorate and die.

Symptoms

1. Fever.
2. Headache.
3. Nausea.
4. Vomiting.
5. Anxiety.

Diagnosis [19-20]

1. Direct fluorescent antibody (DFA) test
2. Fluorescent antibody test (FAT),
3. The direct fluorescent antibody (DFA) test is used to diagnose rabies and looks for the presence of rabies virus antigens in brain tissue.

- Pasteur has successfully developed a vaccine against rabies. Pasteur used the equivalent method he developed for the anthrax vaccine.
- There are two ways to use the rabies vaccine. Rabies vaccines are used for people who come into contact with (for example, biting, scratching, or licking) animals that are known or believed to have rabies. This is called post-exposure prevention. Rabies vaccine can also be provided early to people at high risk of infection with rabies virus.
- These people include veterinarians, animal keepers, or travelers who will stay in a country with a high rabies infection rate for a month, as well as people who live, work, or vacation in wild areas of countries where they may return. Contact with wild animals. This is called pre-exposure prevention.
- Worldwide, approximately 59,000 people die each year from rabies transmitted by dogs.
- In Asia, due to rabies transmitted by dogs, an estimated 35,172 deaths per year (59.6% of global deaths).
- In Africa, the estimated number of human deaths from rabies reported annually is 21,476 (representing 36.4% of global deaths). In Asia, India is the country with the highest number of human deaths from rabies (59.9%) and the world (35%)
- After India and China are the other countries most affected by rabies.Even after huge economic investments, rabies remains a major health problem in Asian and African countries.

1938 - Tetanus Vaccine [21]

- Tetanus is an infection caused by a bacterium called Clostridium tetani. the bacteria enter the body, to produce a poisonthat causes painful muscle contraction. Another name for tetanus is "lockjaw". It usually causes a person's neck and jaw muscles to lock up, making it difficult to open the mouth or swallow.

Symptoms

1. Painful muscle stiffness all over the body.
2. Trouble swallowing.
3. Headache.
4. Fever and sweating.
5. Changes in blood pressure and fast heart rate.

Diagnosis [22]

1. Physical exam,
2. Medical history
3. Vaccination history

- The first active tetanus toxoid was discovered in 1924. A simpler adsorption version of the vaccine, made in 1938, proved successful when it failed to prevent tetanus in the armed forces during World War II.
- Tetanus vaccine, also known as tetanus toxoid (TT), canprevent tetanus. Five doses are recommended for children and six doses are recommended during puberty.
- Almost everyone becomes immunized first after 3 doses, but boosters are recommended every 10 years to maintain immunity.
- The type of vaccination against this disease is called artificial acquired immunity. This type of immunity is generated when a dead or weakened disease enters the body and causes an immune response that involves antibody assembly. This is beneficial for the system to recognize antigens and produce antibodies more quickly when the disease enters the body.
- About 59,000 people died in 2013, down from 356,000 in 1990. Mortality rates in the United States were 91% in 1947, 2131% in 1982 to 1990, 11% in 1995 to 1997, and 18% in 1998 to 2000. Current statistics show that the mortality rate for mild and moderate tetanus is about 6%. In severe tetanus cases, it is as much as 60%.
- The mortality rate in the United States from systemic tetanus is 30% overall, 52% in patients over 60 years of age, and 13% in patients younger than 60 years of age. The mortality rate for people over 60 (40%) is much higher than for people over the age of 2059 (8%). From 1998 to 2000, 75% of our deaths were patients aged 60 years or older.

1955-Polio Vaccine[23]

- Poliois a disabling and life-threatening disease caused by the polio virus. The virus can spread from person to person, infecting the person's spinal cord, causing paralysisand weakness.
- Polio is caused by three types of polio viruses. There is a lot to be spread by face-to-face contact with an infected person. It can also be caused by eating and drinking contaminated food or water. Polio is visible in infants and occurs in conditions of poor hygiene.

Symptoms

1. Fatigue
2. Fever
3. Headache
4. Pain in the arms and legs

Diagnosis[24]

1. Stool specimens
2. Sample of throat secretions
3. Colourless fluid that surrounds your brain and spinal cord (cerebrospinal fluid) is checked for poliovirus.

- The polio vaccine is used for polio. Two types are used: inactivated poliovirus (IPV) given by injection and attenuated poliovirus (OPV) given by mouth. The World Health Organization (WHO) recommends that all children should fully vaccinated against polio.
- The number of annual reported cases in which polio has been eradicated from most of the places. The inactivated polio vaccine is very safe. The injection site may become slightly red or painful.
- The first successful polio vaccine demonstration was in 1950 by Hilary Koprowski using a live attenuated virus to isolate a beverage.
- More than 2,000 deaths occurred in New York City alone, which had more than 27,000 cases and more than 6,000 deaths due to polio in the United States that year.
- Two vaccines are used worldwide to eradicate polio.Salk vaccine or inactivated vaccine (IPV) consists of an injected dose of inactivated poliovirus. In 1954, the vaccine was tested for its ability to stop polio. Its field trials were the most important medical experiments in history.
- In 1955, it was chosen to be used by all of us. By 1957, the annual number of polio cases in the United States had declined from about 58,000 at peak to 5,600.

1967-Mumps Vaccine:[25]

- Mumps is an infectious disease caused by viruses and inflammation of the salivary glands, especially the parotid glands. It is spread by sneezing or coughing due to infection.

Symptoms

1. Discomfort in the salivary glands.
2. Difficulty chewing.
3. Fever.
4. Headache.
5. Muscle aches.
6. Tiredness.

Diagnosis [26]

1. Blood or urine test.
2. Cerebrospinal fluid

- Mumps is caused by an infectious disease. Mumps usually begins with a fever, headache, muscle aches, fatigue, and loss of appetite. After that, most people develop swelling of the salivary glands.
- Although mumps infection in children was not considered a serious public health problem. The first mumps vaccine was approved in 1948. It was developed from an inactivated virus and has only a short-term effect.
- Mumps can be prevented by MMR vaccine. It protects against three diseases like measles, mumps and rubella. The CDC recommends giving children two doses of the MMR vaccine. The first dose is at 12-15 months of age, the second dose at 4-6 years of age. Teenagers and adults are also getting the MMR vaccine so far.
- MMR vaccine is very safe and effective. The mumps component of the MMR vaccine is effective in about 88%.
- Mumps spreads all over the world. Without mumps vaccination, 100-1,000 cases occur per 100,000 people each year. That is, it infects 0.1% to 1.0% of the population each year. The incidence peaks every 2 to 5 years and is highest in children aged 5 to 9 years.

1981-Hepatitis B Vaccine:[27]

Hepatitis B is a serious liver infective diseases caused by the hepatitis B virus (HBV) and Inflammation of the liver. A severe liver infection caused by the hepatitis B virus can be easily prevented with a vaccine. The disease is usually spread through contact with infected bodily fluids.

Symptoms

1. Abdominal pain.
2. Dark urine.
3. Fever.
4. Joint pain.
5. Loss of appetite.

Diagnosis[28]

1. Blood tests
2. Liver ultrasound (transient elastography)

- The hepatitis B vaccine is also known as the first "cancer" vaccine because it can prevent hepatitis B. Bloomberg and Millman developed the first vaccine against hepatitis B, which was originally a heat-treated form of the virus. The first hepatitis B vaccine was approved for use in the United States in 1981. The restructured version was launched in 1986. It is included in the list of essential drugs of the World Health Organization.
- Worldwide, 80% of liver cancers are caused by chronic hepatitis B and C, which is the second most common cause of cancer death. Therefore, a vaccine to prevent hepatitis B infection can also help prevent liver cancer.
- About 1.5 million people are infected each year. Almost 300 million people are chronically infected. 10% of infected people are diagnosed. An estimated 820,000 people die each year from complications such as hepatitis B and liver cancer.

1996-Chickenpox Vaccine:[29]

Highly contagious infectious disease, usually in children, caused by the varicella zoster virus of the genus Varicella. Chickenpox is spread by respiratory secretions or by contact with broken skin.

Symptoms

1. Fever, feeling tired, headache.
2. A stomach-ache that lasts for one or two days.
3. A skin rash that is very itchy and looks like many small blisters.

Diagnosis [30]

1. Polymerase chain reaction (PCR)
2. Visual examination.
3. The use of polymerase chain reaction (PCR) to detect VZV in skin lesions (vesicles, scabs, macular lesions).

- The research team of American vaccinator Maurice Hilleman at Merck invented the chickenpox vaccine in 1981.
- Japan was one of the first countries to vaccinate against chickenpox. The vaccine developed by the Hilleman and first licensed in the United States in 1995. One dose of vaccine prevents 95% of moderate illnesses and 100% of serious illnesses.
- Approximately 400,000 cases occur annually in the United States, mostly children, and generally 10,500-13,000 hospitalizations (range, 8,000-18,000) occur annually, with 100-150 cases Dead. Most children were infected, but most deaths were adults.

1920-Dengue Vaccine:[31]

Dengue is an infection by mosquito virus. Mosquito transmitted and causes sudden fever and acute joint pain. Dengue fever can be very painful, but it is not usually fatal. Dengue spread mainly by some female mosquito species from Aedae named Aegypti Aedes. The Dengue virus is infected with lymph nodes and bone marrow, spleen and hepatic macrophages, and cells containing monocytes in the blood.

Symptoms

1. Nausea, vomiting.
2. Rash.
3. high fever (40°C/ 104°F)

Diagnosis [32]

1. Blood test
2. Urine (routine & microbiology)
3. Chest X-ray

- The Dengue vaccine used to prevent dengue fever was discovered in 1997 by researchers at St. Louis University.
- Dengue viruses are spread to people via the bite of an infected Aedesmosquito. 40% of the world's population, around 3 billion people, sleep in areas at risk of dengue.
- Dengvaxia can be a live but weakened vaccine that works by triggering an immune response against the four dengue viruses. Dengvaxia is a tetravalent vaccine, live, for the prevention of dengue disease caused by serotypes 1 –4.
- The death rate of untreated dengue shock syndrome is sort of 20%. The reported incidence has increased in last 50 years and there are an estimated 5 to 100 million dengue infections worldwide each year, including 22,000 deaths.

2020-Covid 19 Vaccine:[33]

- Coronaviruses are a group of viruses that cause disease in mammals and birds . In humans, coronaviruses can cause respiratory infections, ranging from mild to fatal. Current evidence suggests that the virus spreads, usually within a meter (short distance), primarily between people in close contact with each other.
- People may be infected when they breathe in aerosols or droplets containing the virus or directly touch the eyes, nose or mouth. Coronaviruses are zoonotic, which means they can spread between animals and people. The virus that causes COVID19 belongs to a family of viruses called Coronaviridae.

Symptoms

1. Fever, cough and shortness of breath
2. Loss of taste or smell
3. Sore throat

Diagnosis[34]

1. Rapid diagnostic tests (RDT)
2. Swab Test
3. CT scans
4. Throat (throat swab) or saliva.
5. The polymerase chain reaction (PCR) test

- In humans, coronaviruses can cause respiratory infections, ranging from mild to fatal. Current evidence suggests that the virus spreads, usually within a meter, primarily between people in close contact with each other.
- People could also be infected once they inhale droplets containing the virus or directly touching the nose or mouth. The virus that causes COVID19 belongs to a family of viruses called Coronaviridae
- The benefit of preventing the spread is to understand the COVID19 virus, the diseases it causes and how it spreads, Protection etc. Wash your hands or use alcohol-based disinfectants.
- Covaxin is a COVID19 vaccine based on an inactivated virus, jointly developed by Bharat Biotech and the Indian Medical Research Council.
- In July 2021, Bharat Biotech reported that the vaccine has an effective rate of 64% for asymptomatic cases and 78% for symptomatic cases, The effective rate for symptomatic cases is 93% for severe COVID19 infection, and 65% for Delta variants. On December 6, 2020, Bharat Biotech submitted an application requesting emergency use authorization.
- On January 2, 2021, the Central Pharmaceutical Standards Control Organization (CDSCO) recommended the license, and was approved the next day.
- As of August 19, 2021, 209,201,939 confirmed cases of COVID19 have been reported to WHO globally, including 4,390,467 deaths. As of August 18, 2021, 4,543,716,443 doses of vaccine had been vaccinated.

CONCLUSION

Studies have shown that the benefits of vaccination outweigh the risks, because vaccines can prevent serious illness and disease in people, and vaccination can also prevent the widespread spread of disease in the population. Therefore, although the side effects of vaccination are sometimes serious, they are very rare. The advantage of vaccination is to offset the risk, and the vaccine does that and has eliminated many diseases. For centuries, vaccination has played an important role. People began using Chinese, Turkish and Asian vaccination techniques dating back to 1000 AD. One of the main objectives is to strengthen the scientific basis for the evolution of vaccines and public health care and disease prevention. Although it is generally believed that infectious diseases will be eliminated in the 20th century, in the past 20 years, new and re-emerging infections have appeared in different parts of the world, and their incidence is likely to spread in the future.

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Table No:1-US recommended types of vaccines

Vaccine type	Vaccines of this type on U.S. Recommended
Live/attenuated	Measles, mumps, rubella (MMR combined vaccine) Varicella (chickenpox) Influenza (nasal spray) Rotavirus
Inactivated/Killed	Polio (IPV) Hepatitis A
Toxoid (inactivated toxin)	Diphtheria, tetanus (part of DTaP combined immunization)
Subunit/conjugate	Hepatitis B Influenza (injection) Haemophilus influenza type b (Hib) Pertussis (part of DTaP combined immunization) Pneumococcal Meningococcal
Live, attenuated	Zoster(shingles) Yellow fever
Inactivated/killed	Rabies
Subunit/conjugate	Human papillomavirus

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RESEARCH ARTICLE

CSG: Cloud-Based Smart Garbage Collection System using IOT

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ABSTRACT

A healthy environment is essential for a happy and healthy community. The previous method of employing individuals to inspect and empty full trash cans regularly was prone to human mistakes and negligence. Furthermore, due to the varying frequency of trashcan usage in various locations, regular inspections based on time crevices are wasteful since a dustbin may be full early and need immediate care, or there may be no need for a routine check an extended length of time. As a result, overflowing and smelling dustbins become more of a problem than a solution, rendering the current system resource-intensive and ineffective. This article describes a solution for cloud-based Smart Garbage Collection utilizing IOT-based CSG methods. This article describes the CSG technique for sorting garbage into electronic, non-biodegradable, and biodegradable. When the amount of waste detected reaches a certain level, the CSG system will communicate it to the municipality. The CSG system includes an ultrasonic sensor that measures the bin's volume, an Arduino UNO that controls the system's operation, and a load cell that measures the weight of the bin. Furthermore, the MQ-135 - Gas Sensor is utilized to evaluate air quality. The IoT garbage surveillance system is a very innovative method that helps clean cities. This system monitors the garbage containers and gives information on the quantity of waste collected in the containers on a webpage.

Keywords: IOT, Cloud, Arduino, MQ-135 Gas Sensor, Ultrasonic sensor, waste management.

INTRODUCTION

The internet has become an essential part of our lives in this decade. In this perspective, researchers started combining Internet-based communication and creating the Internet of Things (IoT) [2]. IoT has created a whole new universe of opportunities to simplify and speed up our many daily activities. The Internet of Things (IoT) is a network of connected and interconnected objects that interact and share data [3]. In the Internet of Things, a linked item is a sensor that performs a particular job and may communicate with other connected devices. Waste management is a constantly evolving problem on both the local and global levels. Human and animal actions are often wasteful and unpleasant, resulting in solid waste [5]. Residential trash is collected using rubbish containers at a regular location on a particular road/area. One of the most difficult jobs is the trash bin inspection process for garbage collection. The standard method is to go through different areas and inspect them for trash buildup. This is a complicated and time-consuming procedure. The waste management system is currently not as successful as it could have been given the advancements and technology developed in recent years [4]. Waste collection and handling, particularly in cities, are costly. Because the conventional trash collection technique does not consider the contents of the rubbish container, waste may not be collected on time. This article offers a method for connecting a trash collection system to the Internet of Things. This article utilizes an ultrasonic sensor. Waste collection is not required when the rubbish container contains just light items, such as papers, since these materials may be compressed to accept more trash [6].

MQ-135 aids in the separation of light trash, such as paper, from heavy waste. Smart Bin is a self-aware waste-collecting dustbin that detects the quantity of garbage in a trashcan; it may based on this, transmit warning signals to municipal bodies demanding the replacement of the dustbin. This kind of trash will be extremely helpful in areas where the frequency of individuals using the trash can fluctuates since timely inspections will not suffice [7]. Other features are also included, such as the automatic shutting of the doors with motors utilizing an Ultra-sonic Sensor when the trash is full, which may prevent waste from collecting around the dustbin [9]. IOT-based waste monitoring systems based on ultrasound sensors and MQ-135 is the main objective. The specific objectives are to develop an intelligent bin to detect the garbage weight and volume in the bin, determine the optimum number of ultrasound sensors for measuring volume, and correlate the volume and weight of boxes based on gathered data. The study uses trash monitoring via the placement of an ultrasonic sensor in a specific waste container [10]. A graph and data will be shown to the user through an app. The study will promote adopting a clever bin and its new role in the community by giving users a sense of efficient and cost-effective waste management [14]. The scope of the research focuses on controlling the quantity and weight of the garbage in the bins for generating and predicting waste results based on sensor data [12]. The remainder of the paper is structured as follows: Section II goes through related work. Section III describes the suggested method, while Section VI contains the results. Section V concludes the paper with concluding comments.

BACKGROUND STUDY

Aswin Raaju, V et al. [1] needed a new trash collecting system. The sensors will tell whether or not the dustbins are full. When it is full, the truck driver is given the location of the bins where it was found for pickup. This method removed the current situation with the dustbins, which are deplorable due to the loaded trash and are not being cleaned. A cloud server was also put up, via which the municipal community authorities may get information on the dustbins that are not attended to and are not full. This mission arrived pleasantly, with a helpful clarification for the preservation of the natural environment. Anjomshoaa, A. et al. [2] the urban phenomena that may be recorded using drive-by sensing were described in depth. The FEELS classification was developed to define sensor types and categorize the wide array of possible applications. The authors highlighted the spatiotemporal constraints of distant and stationary sensing, which may be partly overcome by drive-by sensing. The spatial coverage of drive-by sensing was dependent on the movement patterns of the hoisting vehicle.

In recent years, garbage collection has been handled fairly by Chaudhari, S. S., & Bhole, V. Y. [3]. The spread of sensors and actuators also enables dynamic models to be developed. The authors offered a more efficient waste management system based on the internet of things, smart management of all garbage bins throughout the city. They recommended characteristics such as optimizing resources, cost reduction, and time management. Mohan, A. et al. [5] a trash collecting system based on IoT was suggested. The suggested method prevents the irregular cleaning of over-filled bins by providing warnings when the dustbins are full. The cleaning procedure may be remotely monitored in real-time. This method lowers the amount of time spent on trash management and monitoring by humans. As a result, it was more efficient than the previous technique of trash collecting. This method, if adopted, would result in cleaner cities.

Lokuliyana, S. et al. [7] This article combines IOT solutions to build a system that offers a system that better equips the municipal council to manage the trash issue in a smart city. Every party was engaging with this system: citizens, employees, and administrators. This method was primarily designed for a city with a large or increasing population. This system was designed to accommodate increasing populations. Thus the number of bins was raised until the quantity of trash collected could be met. The route computation ensures that the bins never overflow. The government may utilize this method to monitor hazardous materials produced and implement measures to decrease these levels. They may also utilize this method to check that the tactics being used are successful. The government may establish recycling centers, and the profit that can be realized can be estimated. Pawar, S. S. et al. [8] the project intends to provide an IoT-based smart garbage monitoring system. A modest prototype prevents irregular trash pickup by delivering warnings to the appropriate persons through a Web server and SMS. Real-time data may be utilized to improve trash collection efficiency. Savita, K. et al. [11] was primarily intended to avoid overfilling trash containers, which had happened many times on different occasions. The prototype operated as planned due to the user acceptability testing results, with an overall success rate of 80%. Finally, based on the user information, the majority agreed that the prototype 'Smart Event Management Waste Bin' could deal with waste bin overfill and monitor waste bins during an event. Wijaya, A. S. et al. [13] the purpose of this article is to offer a technical method for a waste management system. The writers began with a smart waste bin. The exact real-time data from the existing system may be used using the network environment for an efficient solid waste management system. The technology can collect accurate data that may subsequently be incorporated into a management system in real-time. The load cell calibration technique simplifies calibration, connected without alterations or modifications to a commonly used trash bin.

PROBLEM DEFINITION

Domestic trash is disposed of in dustbins placed along the roadway. This public trash can is emptied at random. Because the dust bins sometimes fill up faster than usual, the overflow level needs constant human supervision. When dustbins overflow, people cannot dispose of their waste in the bin and dispose of it elsewhere. During the rainy season, the problem worsens because rainwater enters the trash, creating foul smells. To minimize overflow and prevent people from dumping their trash outside the bin, This article suggests a CSG smart bin system that can separate electronic waste, bio-degradable, and non-biodegradable wastes, with the waste being put around the bin and the information being transmitted to cloud storage.

CLOUD-BASED GARBAGE COLLECTION USING IOT

With the fast rise in the human population, effective waste management is essential for creating and sustaining an environmentally friendly, hazard-free environment. When the trashcan is overflowing or over-filled, the municipality truck usually comes to pick it up. Important trash information such as height, weight, and odor are not considered. Maintaining these settings guarantees that the work is completed correctly and on schedule. The microcontroller is connected to the height, weight, and ultrasonic sensors. When the sensor readings hit a certain threshold, they are transmitted to the controller, who uploads the data to the cloud for further processing. Following the data analysis, some trash bins with values more than the threshold amount are identified and collected. The most advantageous trash bins must be chosen based on the values, and an optimal route must be calculated. The

optimized route is subsequently sent to the trash collection truck. The customer may get information such as when the trash bin was last picked up using an app. The suggested method is shown in Figure 1 is a block diagram. The wastes are classified into three types: electronic, bio-non-degradable, and degradable wastes. The following components were utilized in the CSG system:

Liquid Crystal Display

LCD screens are electrical display modules with a wide variety of applications. A 16x2 LCD is a very basic module extensively utilized in many devices and circuits. These modules are preferred over LEDs and seven-section LEDs. The reasons are the following: LCDs are cheap, easy to program, and have no limitations for displaying unique characters and even customized ones (as in seven segments), animations, etc. A 16x2 LCD can display 16 characters per line and has two lines of this kind. Each character is displayed on this LCD in a 5x7 pixel matrix. There are two registers for this LCD: command and data.

I2C MODULE FOR 16X2 (1602) CHARACTER LCD

The I2C module has a PCF8574 I2C chip, which transforms I2C serial data into parallel LCD data.

These modules currently have a 0x27 or 0x3F default I2C address. Check the black I2C adapter board at the bottom of the module to identify which version. If you have three sets of A0, A1, and A2 pads, the default is 0x3F. If no pads are available, the default is 0x27. There is a contrast adjustment pot at the bottom of the display. It may be necessary to adjust the text correctly on the screen.

ARDUINO

Arduino is an open-source prototyping platform built on simple hardware and software. It consists of a programmable circuit board and ready-to-use software known as the Arduino IDE (Arduino IDE) (Integrated Development Environment). It is used to generate and upload the physical board computer code

MQ-135 - GAS SENSOR FOR AIR QUALITY

MQ-135 Sensor Features

- Wide detecting scope
- Fast response and High sensitivity
- Stable and long life
- Operating Voltage is +5V
- Detect/Measure NH3, NOx, alcohol, Benzene, smoke, CO2, etc.
- Analog output voltage: 0V to 5V
- Digital output voltage: 0V or 5V (TTL Logic)
- Preheat duration 20 seconds
- It can be used as a digital or analog sensor

The potentiometer may be used to modify the digital pin sensitivity.

The air quality sensor is also a sensor MQ-135 that detects venomous gases in the air in homes and workplaces. Tin dioxide (SnO2) is utilized in the gas sensor layer; it is less conductive than clean hair and increases air pollution conductivity. Air quality sensor detects ammonia, nitrogen oxide, smoking, CO2, and other dangerous chemicals. The air quality sensor includes a small potentiometer for changing the load resistance of the sensor circuit. A 5V power supply powers the air quality sensor.

The air quality sensor indicates the signal output instruction. There are two outputs: an analog and a TTL. The TTL output is a low signal light accessible through the IO ports of the microcontroller. The analog output is a concentration that is proportionate to the increasing Voltage. This sensor has a long service life and reliable stability.

Ultrasonic Module HC-SR04

The ultrasonic sensor uses the concepts of SONAR and RADAR to calculate the distance from the item.

Ultrasound

Ultrasound is high pitch sound waves with frequencies greater than the human hearing limit.Figure 7 represents ultrasound wavelength is referred by using https://lastminuteengineers.com/arduino-sr04-ultrasonic-sensor-tutorial/. Human ears can detect sound waves vibrating between 20 and 20,000 rumbling noises per second (a high-pitched whistling). As ultrasonic is higher than 20,000 Hz, however, it is inaudible for humans. The Ultrasonic distance sensor HC-SR04 is constructed around two ultrasonic transducers. The transmitter is used to transform electric impulses into ultrasonic sound pulses at 40 KHz. The recipient senses pulses transmitted. It produces an output pulse, the width of which may be utilized for calculating the traveled pulse is received. The sensor is small and easy to use for any robotics project. It offers superb non-contact range detection with a precision of 3mm between 2 cm and 400 cm. It operates on five volts; instantly, it may be linked to an Arduino or any other 5V logic microcontroller. This article connects the 5V pin of the Arduino to VCC is an electricity supply for the HC-SR04 Ultrasonic Distance Sensor.

It all starts when the trigger pin has a pulse of 10 S (10 microseconds). The sensor then transmits a 40 KHz eight-pulse sound burst. This 8-pulse pattern differentiates between the ultrasonic signature of the device so that the transmitted pattern may be distinguished from ambient ultrasonic noise. The eight ultrasonic pulses travel away through the air from the transmitter. In the meanwhile, the Echo pin rises high, indicating the beginning of the rear signal. If the pulses are not reflected, after 38 mS, the signal will delay and return low (38 milliseconds). A 38 mS pulse thus does not indicate any obstruction within the sensor range. The ultrasonic sensor produces a high-frequency sound wave after collision with an obstacle and waits for the reverse. To determine the distance, the time it takes for the wave to travel back and forth. When the reflected wave is received, the distance is measured and shown on the LCD screen. At the same time, the data is sent through GPRS to the website. The load cell sensor detects the waste weight in the trash bin and sends it to the Arduino. The weight is shown on the LCD screen. At the same time, data are sent to the website through a GPRS connection. The Thingspeak IoT platform provides ultrasonic sensors and MQ-135 (load cell), which refresh the channel. The trash monitoring system includes ultrasonic sensors for waste bin level and cell load sensors for waste bin weight. The sensitivity of resistance variations in the load cell sensor is too low to detect by the Arduino. As a consequence, an amplifier module amplifies the signal of resistance changes in the load cell sensor.

DISCUSSION

The following are the outcomes of this research.

- Detection of waste levels inside the trash.
- Wirelessly transmit the information to the concerned party.
- Data may be accessed at any time and from any location.
- Data transfer and access in real-time.
- Prevents the trash from overflowing. This IoT-enabled trash management is very beneficial to smart cities in a variety of ways. This article has observed that various dustbins are placed in different cities, and dustbins often overflow, and the concerned individuals are not informed. This solution is intended to solve this problem by providing comprehensive information about the dustbins located around the city. The designated authority may

access the information from anywhere and at any time. The pulse width is then used to calculate the distance from the reflected element. This may be computed using a fundamental equation of distance speed.

Show an example to see what I mean. See what I mean. Suppose this item has an unknown distance object in front of the sensor and the pulse on the Echo pin is 500 S broad. Let's find out how far from the sensor object. This article uses the following equation.
Distance = Speed x Time
It has the time value 500 s, and to know the speed.
Distance = 0.034 cm/µs x 500 µs
But it's not done! Remember that the pulse represents the time it takes for the signal to be transmitted and reflected to reach the distance.
Distance = (0.034 cm/µs x 500 µs) / 2
Distance = 8.5 cm

CONCLUSION

A CSG-Cloud-based IoT-based intelligent trash collection system guarantees that waste may be cleansed when the waste level peaks. If the garbage is not cleaned for some time, a record will be sent to the higher authority, which will take action against the official responsible. This approach also helps to detect erroneous reporting and reduce corruption in the management system as a whole. It eventually contributes to the preservation of cleanliness in society—the split management, which aids in determining whether or not the trash, is full. In terms of creativity and concept, this is a major project. This article uses the Internet of Things idea, which provides this project its charm and originality in terms of the concept. The concept aims to clean the locations where garbage bins are situated and the very basic administration. Its goal is to provide sophisticated administration of the whole trash collection system. This article utilizes ultrasonic sensors and other hardware microcontrollers and processors such as Arduino to evaluate trash levels and transmit information to administrators. Then, trash trucks are sent by them. Another critical element of this concept is the online portal, which has been developed. Both operators and people would find it easy to monitor trash information from different locations. As a result, an IOT Cloud-based software project using electronic devices will provide a tremendous service to the world and, to some degree, make it a better place to live.

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Table 1. Pin Configuration

Pin No:	Pin Name:	Description
Module		
1	Vcc	It is used to power the sensor; the operational Voltage is often +5V.
2	Ground	To connect the module to the ground of the system.
3	Digital Out	You may also utilize this sensor to get digital output using the potentiometer from this pin by defining a threshold.
4	Analog Out	This pin generates an analog Voltage of 0-5V depending on the gas intensity.
Sensor		
1	H -Pins	The two H pins are linked with one pin to the supply and the other to the ground.
2	A-Pins	The A pins and B pins may be exchanged. These pins are linked to the Voltage of supply.
3	B-Pins	A pins and B pins may be exchanged. One pin is the output; the other is pulled to the ground.

Table 2: Data displaying in the cloud for garbage monitoring with various locations

Sno	binno	biodeg	co2	nonbiodeg	e-waste	location	date
1	1	44	12	60	28	11.018574,76.966197	7/19/2021 19:40
2	2	24	8	12	56	11.016202,76.965874	7/19/2021 19:50
3	3	72	12	32	84	11.015323,76.963424	7/19/2021 20:06
4	4	88	35	68	24	11.020607,76.960964	7/19/2021 20:16
5	5	24	52	76	48	11.011939,76.959541	7/19/2021 20:27
6	1	48	20	72	56	11.018574,76.966197	7/19/2021 20:56
7	2	28	16	64	36	11.016202,76.965874	7/20/2021 8:58
8	3	80	45	32	60	11.015323,76.963424	7/20/2021 11:14
9	4	88	12	72	24	11.020607,76.960964	7/20/2021 11:16
10	5	24	17	80	64	11.011939,76.959541	7/20/2021 11:18

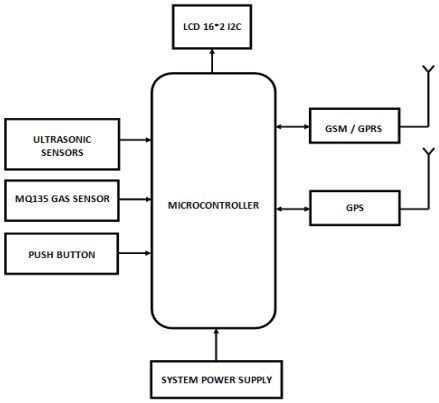

Figure 1: CSG Block Diagram

Figure 2: LCD Module

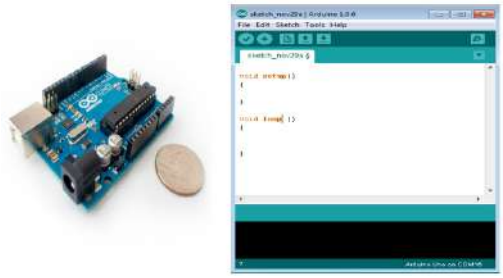

Figure 3: Arduino display

Figure 4: MQ-135 Gas Sensor/Module

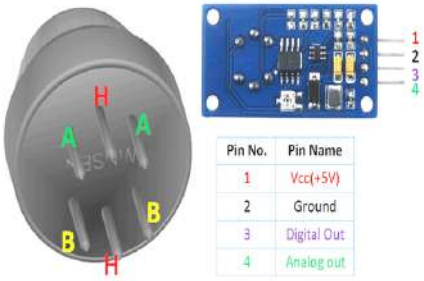

Figure 5: MQ-135 Gas Sensor Pinout

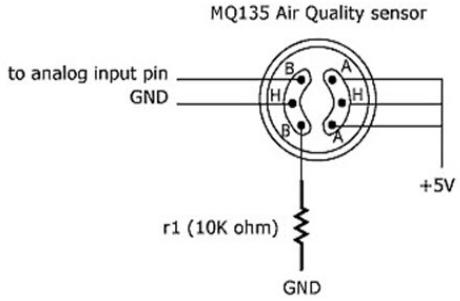

Figure 6: MQ-135 Sensor input and power supply details

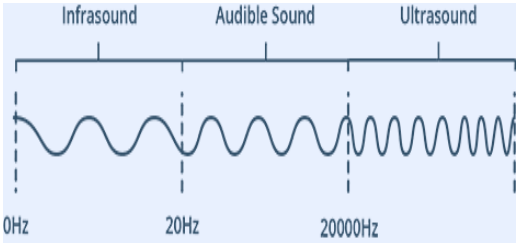

Figure 7: Ultrasound wavelength

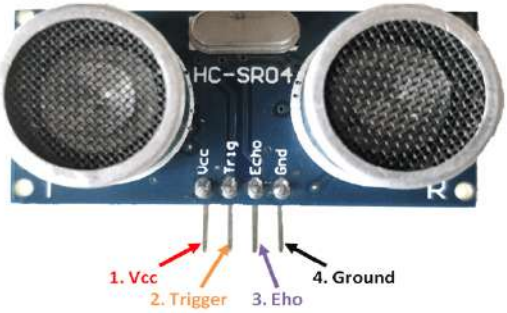

Figure 8: Ultrasonic sensor

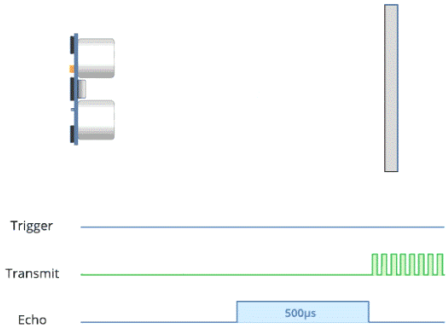

Figure 9: Ultrasonic sensor Trigger and Transmit and Echo level description

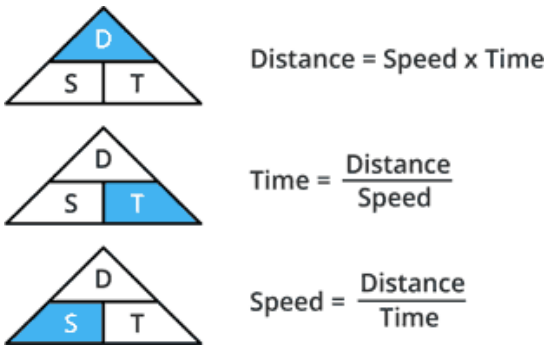

Figure 10: Equation for DST.

Figure 11: CSG Dust Bin waste monitoring in percentage

Figure 12: Waste segregation unit

Figure 13: CSG smart Bin

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RESEARCH ARTICLE

Prospective Review on Cyber Bullying Recognition Techniques on Social Media using Machine Learning

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ABSTRACT

With the more pervasive use of technology, the dominance of cyber bullying has increased. Cyber bullying is an activity of sending threatening messages to insult person. Cyber bullying has resulted in such disastrous consequences; there is a vital need to detect it. To prevent cyber victimization from the activity is not easy. Research into cyber bullying detection has expanded lately, due partially to the explosion of cyber bullying thru social media and its impeding impact on youngsters. These approaches use machine learning and natural language processing methods to detect the features of cyber bullying interchange and automatically detect cyber bullying by corresponding verbatim data to the identified traits. In this paper, we present an efficient review of published research on cyber bullying detection approaches.

Keywords: Cyber Crime, Cyber bullying, Social Media, Machine Learning, NLP, Text Classification.

INTRODUCTION

Internet users from all over the sphere utilize and access varieties of Social Media and Social Network Services (SNS) as a fundamental of their personal networking, relationship collaboration, transferring and sharing of knowledge within the communities. To discuss on this, further, the term Online Social Networking is defined as Social Media

(SM) that has been used to develop Social Networks. Also, the sites that provide Online Social Media services assists users in forming an impression or perception, in maintaining and procuring new relationships in the social network. It can found that SNS clients meet others through internet based local area in genuine and virtual world in the internet, permitting clients to show their interpersonal organizations plainly and keep up with association and systems administration with others.SM has become communicated mode for some bloggers to communicate the data through contributing to a blog. Also, that developed as a problematic stage that is intended for the clients to communicate their day by day exercises, sentiments and assessment by posting basic tweets (messages) inside their companion's network. The dramatic growth of social media during the last years has been associated with the rise of new bullying types. Platforms such as Facebook, Insta, YouTube, Twitter and others are now privileged ways to disseminate all kinds of information. Indeed, connecting through social media devoid of revealing the actual personality has emerged an ideal surface for cyber bullying, where people can throughout their disgust. The topics range from day to day activities in their life to current events, experience sharing, personal opinions and other interests. The SM's such as Facebook, Insta, Twitter, YouTube, MySpace etc., has considerably embarked the way of sharing the facts across the sphere. The emergence of these SMs has caused an increase in cyber bullying circumstances, particularly among the teenagers[4]. Hence, it is important to identify the cyber bullying event and the attacking messages in social media.

Cyber Bullying: Overview

Cyber bullying has been a constant topic within modern day society. It has become an unavoidable problem due to the accessibility of cell phones, computers, and the internet. This problem deserves more attention, because cyber bullying can have detrimental effects on victims. Research has shown that cyber bullying has repeatedly been related with suicidal thought/behavior, along with other matters pertaining to mental wellbeing [5]. This can influence adults and adolescents, but adolescents are more likely to be affected by the harmful effects of cyber bullying [7]. This is real even if the bullying only occurred for a short duration. Even though Platform to be stabilized with automated models, it is important that young people know how to guard against cyber bullying, and from the aggressive communication that can occur online. They are a vulnerable population, and they need to be provided with tools to effectively respond.

Bullying is a foremost problem in today's world and occurs at many diverse ages and in many diverse forms. With the raise in the use of technology, a disturbing trend global is cyber bullying, where individuals can annoy others online through emails, text messaging, and social media websites 24 hours a day, seven days a week. The anonymity cyber bullying offers gives bullies a sense of power and control that else might not be extant if they were face-to-face with their sufferers. Also, the incidence of this topic in current news and media can be endowing to an individual because of enlarged publicity, even if he or she is the only one aware he or she is the bully in question. Thus, it motivates to create a model, i.e. the Cyber Bullying Recognition Model on SMs, with the key role to efficiently determine the cyber bullying associated texts from Comments and providing sound solution thereafter. With this model, the Platforms can categorize the cyber bullying linked comments based on the keywords. By doing this, it allows platforms to normalize the identities of the cyber bullies and the sufferers from the cyber bullying contents in comments.

LITERATURE REVIEW: AN EMPIRICAL STUDY

In this section, we present the most relevant works conducted in cyber bullying detection. After conducting systematic searches and relating the inclusion criteria, different studies were included. In [4] a model was proposed for detecting cyber bullying in social media in particular to Indonesia, model consists of several stages from data cleaning to classification. For Classification Naïve Bayes classification uses Machine Learning WEKA and achieved 86.97% of result that the content having bullying and also 61.63% of psychology type of cyber bullying is attained. Log Data from Twitter used as Data which is processed through Data Cleaning for structured Data, next processed TF-IDF weighting and validation and at last phase data are classified (as shown in fig 1). Data Collected in JSON file and changed to CSV for preprocessing. Preprocessing done both manually and using WEKA tool. Then do Data

validation using 10 Fold Cross Validation from machine learning WEKA. And then do classification using Naïve Bayes on WEKA, to the positive content of bullying going on Group on class result bullying, and the negative content to group on class result negative.

In [5] a systematic review has been directed with the object of survey the researches and studies that have been conducted so far by the research communal in the matter of cyber bullying classification founded on text verbal. It made a choice to focus more on techniques that adopted neural networks and machine learning algorithms. It was found that the best accuracy was achieved when a deep learning approach is used particularly CNN approach. It was found also that, SVM is the most mutual classifier in both Arabic and Latin languages and outperformed the other classifiers. Also, the most widely used feature is N-Gram especially bigram and trigram. Furthermore, results show that Twitter is the main source for the collected datasets, and there are no unified datasets. There is also a shortage of studies in Arabic texts for cyber bullying identification in contrast with English texts. In [6] a study implements a quantitative and qualitative approach to evaluate the Internet associated activities of female residing in several parts of Chennai city between the ages of 17 to 40 years and also gets actions to create consciousness on the safe and unsafe practice of handling their online space. WEKA data analysis tool used to apply the data mining techniques. WEKA holds tools for data preprocessing, classification, clustering, regression, association rules, and visualization. The visualization tool is used to fetch out the suggestion between the female based on the categories and the responsiveness which they have on cyber annoyance. The classifications are made to carry out the better knowledge and thoughtful of the respondents about how they achieve their cyber space based on the scholastic stream and depending on the environment they work (as shown in fig.2).

In [7] a study fundamentally maps out the state-of-the-art in cyber bullying recognition research and serves as a source for scholars to determine where to best direct their future study efforts in this field. Here features categorized into 4 broad groups, namely, content-, sentiment-, user and network-based features. And define content-based features as the extractable lexical things of a document such as profanity, keywords, pronouns and punctuations. Emotion-based features are those features that are indicative of emotive content; they are generally keywords, phrases and symbols (e.g. emoticons) that can be used to regulate the sentiments expressed in a document. User based features are those characteristics of a user's profile that can be used to sort a judgment on role played to the user in an electronic exchange and include gender, age and sexual orientation and finally, network-based features are custom metrics that can be mined from the online social network and contain items such as number of followers, number of friends, frequency of posting, etc. Furthermore, also categorized based detection techniques such as supervised learning techniques, lexicon-based systems, rule-based systems, mixed-initiative systems based on the type approaches employed by the studies and finally, another category for approaches that do not fit into any of the above-listed classes.

In [8] an application was developed a systematic cyber bullying detection model to detect, identify, and classify cyber bullying activities from the large volume of streaming texts from OSN services. Texts are fed into cluster and discriminate analysis stage which is able to identify abusive texts. The abusive texts are then clustered by using K-Mean. Naïve Bayes is used as classification algorithms to build a classifier from our training datasets and build a predictive model proposed by an algorithm that includes two methods, first method is to create partition by repeated relocating from whole datasets into clusters using k-mean clustering and second method is to capturing any specific division with the occurrence of words with multinomial model feature vector and depiction the possibility of words occurring in a document for predict the eight classes(as shown in fig.3). This paper enhanced the Naïve Bayes classifier for extracting the words and examining loaded pattern clustering. In [9] an application was developed using python and web technologies; the system is trained with a set of dataset. First, pre-process the data and then transferred to TF-IDF. Then with the help of Naïve Bayes, SVM (Support vector machine) and DNN algorithm trained the dataset and generate model separately. Then developed a web based application using FLASK framework. Fetch the real time twitter tweets and then apply generated model to these fetched tweets and check the text or images are cyber bullying or not. For these all-purpose python used as code behind, MYSQL is database and

UI designed with HTML, CSS, and JavaScript etc. The main aim of this study is that it presents a system to automatically detect signs of cyber bullying on social media, including different types of cyber bullying, covering posts from bullies, victims and bystanders.

In [10] a classification model was constructed with most favorable accuracy in identify cyber bully conversation using Naïve Bayes and Support Vector Machine (SVM) then apply n-gram 1 to 5 for the number of class 2, 4, and 11 for each method. The purposes of data balancing on the classification of 2 classes cyber bully, non-cyber bully), 4 classes (non-cyber bully, cyber bully level severity low, cyber bully level severity middle, cyber bully level severity high), and 11 classes (non-cyber bully, cyber bully level severity 1 – 10), then the data used amounted to 1.600 for balancing data (800 labeled cyber bully and 800 labeled non-cyber bully) with the following allocation: 2 Class: each class amounts to 800 data, 4 Class: each class amounts to 240 data, 11 Class: each class amounts to 80 data. The most optimal SVM kernel in classifying cyber bullying is the Poly kernel with a standard accuracy of 97.11%, because of the data used in this study are non-linear separable. In [11] suggest a valuable technique to detect and grade the most dominant persons (predators and victims). It simplifies the network communication problem through a projected graph model for detection. The evaluation results indicate that this technique is highly accurate. Besides identifying victims and predators, this graph model can be second-hand to answer many important queries such as how many victims associate to the same predator. Furthermore, ranking methods are employed to identify the most dominant persons on the social network. The feature selection is a key step to represent data in a feature space as an input to the method. Feature selection methods: Common Features and Sentiment Features (as shown in fig.4). LibSVM was applied for classification into bully or non-bully class using a linear kernel and 10 fold cross validation was performed.

In [12] performed cyber bullying detection using a novice approach on Tweets using NLP (Natural Language Processing) and Machine learning techniques. After processing a tweet, it can be flagged down if the tweet is a potential cyber bullying threat. A hybrid approached for sentiment analysis of the tweets, which will help in identifying the highly negative tweets and their subject, which will aid us in flagging down the cyber bullying tweets. Our model consists of three main steps, which includes knowledge based sentiment analysis, whose result is then reinforced with machine learning based analysis. The resulting polarity is then aggregated with the polarity obtained from the emoticons, which segregates the tweets into varying levels of '+'ve and '–'ve text. Analyzed that Lexicon-based methods don't depend on training data and also they provide as advantage with identifying polarity of a sentence. Lexicon-based approaches have been majorly used on conventional text but hardly on Twitter based text as it is difficult to process.

CONCLUSION

So far, not many research works done to identify and detect the behavior of cyber bullying on social networks. Cyber bullying has become a hazard in social networks and it requires broad research for recognition and classification over web users. This paper presents a concise outline about various approaches used for recognition, classification of cyber bullying in SM's and its effects on web users. Automatic detection of cyber bullying would improve restraint and allow responding quickly when necessary.

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Table 1 Literature Study.

Article	Methodology	Phases	Pros & Cons	Inference
[4]	Naïve Bayes classification uses Machine Learning WEKA and achieved 86.97% of result that the content of bullying and also 61.63% of psychology type of cyber bullying is attained.	Model consists of several stages from data cleaning to classification. Data Cleaning for structured Data, next processed TF-IDF weighting and validation and at last phase data are classified.	**Pros:** This research focused towards to analyze how much cyber bullying in Indonesia, development on twitter and to find out the majority type used for cyber bullying by abusers to do the bullying. **Cons:** This research used Twitter Log as the only Data Source.	Log Data from Twitter used as Data. Model Processed with various phases from data collection, preprocessing, TF-IDF weighting, data validation and classification using Naïve Bayes Classifier. It categories the majority type used for cyber bullying by abusers to do the bullying.

[5]	Systematic review has been flowed with the aim of survey the research and study that have been conducted so far by the research community in the concept of cyber bullying classification based on text language.	The main parts of the review methodology (research strategy, quality evaluation criteria) were outlined. Data Sources, Inclusion and exclusion criteria, Search strategy, Quality assessment evaluation. In particular to Arabic & Latin languages content processed for analyzing cyber bullying.	**Pros:** Organized papers based on the selected language, either Arabic or Latin, and both the features and the classification used in both cases. **Cons:** Papers consent only about Deep Learning techniques on Arabic & Latin Language Bullying. Not given concern on type classification.	Different methods are used to detect cyber bullying such as machine learning techniques, Natural Language Processing (NLP), and Deep Learning (DL). Examples of several NLP models [14] like Bag of Words (BoW), Latent Semantic Analysis (LSA) and Latent Dirichlet Allotment (LDA) used to identify bullying in Social Networks.
[6]	A study of quantitative and qualitative approach to evaluate the Internet associated activities of female residing in several parts of Chennai city between the ages of 17 to 40 years.	Research approach through different phase from preprocessing to Visualization. WEKA data analysis tool used to apply the data mining techniques. Weka holds tools for data preprocessing, classification, clustering, regression, association rules, and visualization.	**Pros:** This study depicts various protective measures to be handled by female on their cyber space to protect themselves from cyber stalking. **Cons:** The model ends up at visualizing. This is purely based on survey data. Survey target only certain age group people and only at particular location.	Data sourced through survey conducted between female of ages 17 - 40 years who are residing various parts of Chennai. Max of people attends to a cyber bullying in different medium. It is a measure to create knowledge on the safe and unsafe observed for handling their online space.
[7]	A systematic study of published research (as identified via Scopus, ACM and IEEE Xplore Bibliographic databases) on cyber bullying detection approaches. On the basis of our broad literature review, we categories available approaches into 4 main classes, namely; supervised learning,	Study paper essentially maps out the state-of-the-art in Cyber bullying detection research and serves as a resource for researchers to determine where to best direct their future research efforts in this field. It categorizes features used across	**Pros:** Use of timestamps as features will increase in cyber bullying detection research especially as time information is easily accessible in all forms of electronic communication. **Cons:** Studies majorly included in this survey are supervised learning techniques to detect	Intent and power differential are two key components of bullying that have proven difficult for researchers to demonstrate within an electronic context. Prior to the determination of these two components, however, is the recognition of the victim. To recognize bullies and victims

	lexicon based, rule based and mixed-initiative approaches.	the studies into 4 main groups, namely; content, sentiment, user and network-based features.	cyber bullying. Purely Text based bully identification techniques applied.	within the network based on the frequency and offensiveness of messages exchanged.
[8]	Developed an automatic cyber bullying recognition system to detect, identify, and classify cyber bullying activities from the large volume of streaming texts from OSN services. Texts are fed into cluster and discriminate analysis stage which is able to identify abusive texts. The abusive texts are then clustered by using K-Mean. Naïve Bayes is used as classification algorithms to build a classifier from our training datasets and build a predictive model.	Enhanced the Naïve Bayes classifier for extracting the words and examining loaded pattern Clustering is used. The algorithm follows two models: (1) creating partitions by repeated relocating from whole datasets into clusters using k-mean clustering and (2) define any specific partition with the occurrence of words with multinomial model feature vector and drawing the possibility of words occurring in a document for predicting the eight classes.	**Pros:** Four major Steps: 1) Preparing dataset, data sources comes from the Cyber Crime Data and Twitter across cluster networks from data streams. 2) Generating clusters, data sources are clustered the features two categories of the messages as polite messages and abusive messages. 3) Training data, the abusive partition is used to transform each into the feature extractor for classification technique using on Naïve Bayes. 4) Predicting data and producing predicted labels in eight categories. **Cons:** It is used Cyber Crime Data which is a manually labeled dataset and Twitter as like earlier research.	It classify abusive messages from sentences frequency by using statistics score and partition data sources, and it is capable of classification and prediction model from the feature sets into eight sub categories as; activities approach, communicative, desensitization, compliment, isolation, personal information, reframing, and relationship.
[9]	Application developed using python and web technology. Web based application using FLASK framework. Fetched the real time twitter tweets and then apply generated model to these fetched tweets and check the text or images are cyber bullying or not. For these all-purpose python used as code	Model constructed following below steps first a search to find the dataset downloaded to train the model. After downloading pre-processed the data and then transferred to Tf-Idf. Then with the help of naïve bayes, SVM (Support vector machine)	**Pros:** Techniques of detection applied here are Textual Based and Non Textual Based. Grouped features such as cyber bullying profanity, keywords, pronouns, n-grams, Bags-of-words (BoW), TFIDF (Term Frequency Inverse Document Frequency), spelling content and document length features. Attempt of	The main goal is to recognize the cyber bullying model, help to improve physical monitoring for cyber bullying on social networks. Identify the bully using both Textual and Non textual data from tweets are processed.

	behind, MYSQL is database and UI designed with HTML, CSS, and JavaScript etc.	and DNN algorithm we train the dataset and generate model separately.	cyber bullying detection within media forms like images, animations, and videos using OCR. **Cons:** To improve the system developed by use more accurate dataset and to detect the cyber bullying or not.	
[10]	Constructed a classification structure with reliable accuracy in recognizing cyber bully conversation using Naive Bayes method and Support Vector Machine (SVM) then apply n-gram 1 to 5 for the number of class 2, 4, and 11 for each method. Naive Bayes yields an accuracy of 92.81%, SVM with a poly kernel yields an accuracy of 97.11%. It resulted that SVM with poly kernel yields greater accuracy than SVM with other kernels, like Naive Bayes, and Kelly Reynolds research models of decision tree (J48) and k-NN.	Phases of Model: 1) Preprocessing: Includes Data Cleaning and Data Balancing. 2) Feature Extraction: The preprocessed text will be transformed into a vector space model where texts are presented with a vector of extracted features. 3) Classification: the classification will use the Naïve Bayes & SVM method with linear, poly, RBF, and sigmoid kernels. Each conversation will be a form of questions and answers is combined into one text conversation. 4) Evaluation: To evaluate the classification model based on the exactness can be measured from the accuracy of the model in classification with the method of confusion matrix.	**Pros:** The finest SVM kernel in classifying cyber bullying is the Poly kernel with an accuracy of 97.11%, because of the data used in this study are non-linear separable. Therefore, the optimal function for separating the sample into different classes is SVM with poly kernel. The application of n-gram may increase the accuracy level in cyber bullying classification, due to the highest accuracy level at n-gram 5 (92.75%), the lowest accuracy set at n-gram 1 (89.05%). **Cons:** Pre-processing spend with more time on data cleaning even though there is possibility of unstructured data. Furthermore there may go for choice of algorithm with better optimizing.	Even Data Cleaning done with Excel for eliminating characters under 15letters. Data balancing on the classification of 2 classes (cyber bully, non-cyber bully), 4 classes (non-cyber bully, cyber bully level severity low, cyber bully level severity middle, cyber bully level severity high), and 11 classes (non-cyber bully, cyber bully level severity 1 – 10). Using Confusion Matrix the accuracy of the classification is understood.
[11]	Proposed a novel statistical recognition	The proposed methodology is a	**Pros:** The evaluation metrics	LibSVM was applied for classification into

	method, which proficiently identify concealed bullying features to improve the classifier performance. Then presented a graph model to spot connection between different users in the form of predators and victims.	hybrid approach. It employs sentiment analysis to classify given entry into 'bully' or 'non-bully' category and uses link analysis to find the most influential person.1) Feature Selection: Proposed two feature selection methods: Common Features and Sentiment Features. 2) Victim and Predator Identification: In a network, predators and victims are linked to each other via sent and received messages and identified by their usernames. 3) Cyber Bullying Matrix: to identifying predator and victim based on their respective scores, formulate a cyber bullying matrix (w).	show that feature selection improves the accuracy of classifier, thus reducing resource usage significantly. In addition, it employs the HITS algorithm to calculate scores and grade the most dominant persons (predators or victims). **Cons:** It mainly concentrates on the direct bullying. Indirect Bullying is given as a future enhancement.	bully or non-bully class using a linear kernel and 10 fold cross validation was performed. To identify the predator and victim, HITS algorithm is implemented by computing their respective scores. A predator and victim identification graph is developed for a scenario. Only the messages identified as bullying are considered.
[12]	A hybrid approached for tweets sentiment analysis which will help in identifying the highly negative tweets and their subject, which will aid us in flagging down the tweets which are cyber bullying. Framework consists of three main steps, which includes knowledge based sentiment analysis, whose result is then reinforced with machine learning based	Step 1: Captured the live data from Twitter for building our training dataset. Step 2: The data is segmented into emoticons and text, which are then processed separately. Step 3: The textual data in each tweet is processed separately using a two pronged strategy. The first	**Pros:** This hybrid approach helps us reinforce our results such that it does not violate an individual's freedom of speech. Three polarities for each sentence: (1) Sentiment from Emoticons Analysis (2) Sentiment from Knowledge Based Approach (3) Sentiment from Machine Learning Approach.	Tweets are segmented into Emoticons and Text. Identified Emoticons checked whether emoticons are positive or negative. Identified the tweet polarity using Emoticons as noisy labels. Analyzed that Lexicon-based methods does not depends on training data and also they provide as advantage with identifying polarity of a

	analysis.	strategy is the knowledge based approach. Same is processed through ML Algorithm. Step 4: Final step is is Polarity Aggregation	**Cons:** The use of this algorithm can be extended to other social media platforms like Facebook and Instagram, which do not conform to a fixed number of characters, unlike Twitter, which is a microblog. Vernacularlanguages can also be included once a comprehensive dictionary of their meaning and polarity has been made.	sentence. Lexicon-based approaches have been majorly used on conventional text but hardly on Twitter based text as it is difficult to process.

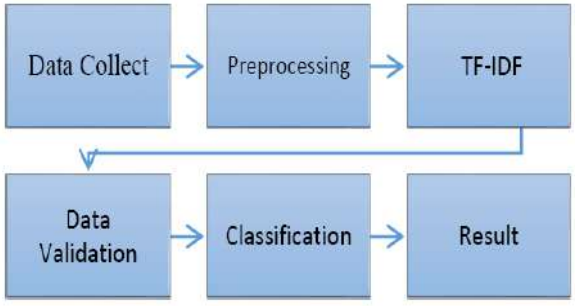

Fig .1. Research Work Flow

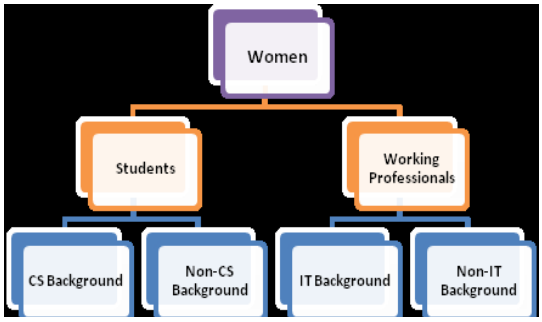

Fig.2. Classification of Women observed from the survey

Categories	Sentences
activities approach	"Are you safe to meet"
communicative	"I just want to meet and mess around"
desensitization	"if I don't cum right back"
compliment	"You are a really cute girl"
isolation	"Do you have many friends"
personal information	"Oh girl, sexy so u wanna talk about underware??????//"
reframing	"Let's have fun together"
relationship	"are you married yet"

Fig 3. Eight Label Categories

	MySpace Dataset				SlashDot Dataset			
Features	Cases	Bully	NonBully	Accuracy %	Cases	Bully	NonBully	Accuracy%
	Sentiment features				Sentiment features			
500	740	15	725	97.97	2174	11	2163	99.49
1000	1034	28	1006	97.29	2868	18	2850	99.37
2000	1383	40	1343	97.11	3380	26	3354	99.23
4000	1657	50	1607	96.98	3808	34	3774	99.11
6000	1766	57	1709	96.77	3945	43	3902	98.91
14000	1934	65	1869	96.64	4067	48	4019	98.82
	Common feature				Common feature			
15632	1947	65	1882	96.61	4077	48	4029	98.85

Fig.4 Classification based on common and sentiment features

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REVIEW ARTICLE

A Review on Misuse of Over the Counter Drugs and Prescription Drugs

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ABSTRACT

Self-control practices and self-service are essential components of any health system. The use of overlapping drugs (OTC) is a part of the self-found process. The popularity of the use of OTC drugs among patients can increase the potential for OTC drug abuse. With pharmacists, as they are accessible, as they are often the first line of contact for patients and have the opportunity to educate and advise patients with the correct use of OTC drugs. The presence of a pharmacist guarantees a safe and effective use of OTC drugs. Pharmaceutical products can connect with other health care providers in the management of autocote practices by patients

Keywords: No Recipe, Behind dtecounter, Self-medication

INTRODUCTION [1-8]

Medicines obtained from patients for the treatment of common diseases, without a doctor's prescription, are known as Surversay (OTC) or prescription drugs. OTC drugs provide prevention and treatment for a wide range of conditions, including, among others, headaches, common cold, musculoskeletal pain, allergies, tobacco dependence, and stomach acidity. However, there is always a risk involved in the use of OTC drugs. These include inadequate self-diagnosis, inadequate dose, prolonged addiction problems, adverse reactions, and medicine interactions, since most patients do not discuss their bench-top drugs with a doctor, they are not aware. OTC Drug abuse for this review is defined as the use of drugs not subject to prescription for non-material purposes. Abuse is often intentional, unlike the abuse of bench-top drugs, which can be the drug used for medical purposes, but in an incorrect way used, for example, lack of knowledge of interactions, inappropriate use of drugs, and the incorrect duration of use.

Aim and Objectives

Drugs, autodestos The sale of drugs on pharmacies' sober (OTC) drugs can help people's self-management symptoms. However, some OTC drugs can be abused, with dependence and damage becoming more recognized.

Places in Use [9-13]

People use potentially addictive prescription or OTC drugs in the following ways:
As an additional drug to use when DOC is not available on the streets.
How reinforcement for intense high.
They tend to be younger (when the stimulants are doc).
They tend to use opiates.
They tend to use prescription and OTC medications in combination with alcohol as a vehicle for suicide.

Buses Drug During the Covid19 Pandemic [14-23]

The Covid19 epidemic has questioned public health policies due to additional concerns about drug addicts and people with foam. Individuals of this vulnerable category could be exposed to additional risks, such as physical problems without fissa dwelling; imprisonment; Price increases for consumers in the black market; and purity reductions. These problems, in combination with a general economic loss, can promote changes to more risky drug behavior, such as:

- Use of substances produced at national level;
- The use of prescription/drugs OTC;
- Mix with less expensive drugs and synthetic cannabinoids.
- Access to drugged services is interrupted by quarantine, social spacing and other restrictive measures adopted to stop the propagation of Covid19.

Pharmacists Document on Drug Prevention, Education and Assistance of Drug Abuse [24-27]

Since multiple users revolve from drugs gradually prescribed / OTC products, pharmacists must increase their surveillance by providing drugs and be both to both potential medicines In the black market.

Pharmaceuticals must participate in open communication to provide tranquility to patients and develop a relationship of trust, especially in vulnerable populations that could be less confident to communicate the entertainment and improper use of health professionals. Pharmaceuticals can help identify patients who can have problems related to substance abuse, and will send them to the appropriate service .

Adolescents and Young Adults [86,88-92]

Prescription drug abuse is highest among 1825-year-olds, with 14.4% reporting non-medical use in the past year. Among adolescents between the ages of 12 and 17, 4.9% said they had not taken any prescription drugs in the past year. The NIDA's Future Survey on Drug Use and Attitudes for Adolescents found that about 6% of high school graduates reported using the prescription stimulant Adderall® last year, and 2% reported abuse of the opioid painkiller Vicodin last year, although this is not the last medical year. Teens who abuse prescription drugs are also more likely to report using other drugs. Multiple studies have shown that there is a link between prescription drug abuse and higher levels of smoking; heavy intermittent drinking; and the use of marijuana, cocaine, and other illegal drugs among American teenagers, young adults, and college students.

Older Adults [34,35]

More than 80% of elderly patients (57 to 85 years old) take at least one prescription drug per day, and more than 50% of older people take more than five drugs or supplements per day. This can lead to health problems due to unintentional use of prescription drugs over the counter or intentional non-medical use.

Data from the National Institute on Drug Abuse.[39]

Commonly abused prescription drugs difficult to detect these drugs because the Federal Department of Transp5ortation's drug testing team or standard forensic drug testing teams may not be able to detect some of these substances, including oxycodone. Sedatives Barbiturates are commonly used as sedatives and anticonvulsants, but they play an equal role in reducing the likelihood of seizures and other symptoms during withdrawal from alcohol, heroin, and other types of drugs. They are addicted, but they develop tolerance; withdrawal syndromes include agitation, headache, psychomotor retardation, confusion, and possible seizures. One response to inadequate treatment is drug addiction in people with legal non-cancerous pain. A recent doctor survey on drug abuse showed that doctors regarded the 4 distraction mechanisms as

(1) visits to a doctor to find a cooperating doctor;

(2) purchasing controlled drugs from multiple doctors;

(3) doctors To deceive or manipulate the patient;

What is prescription (Rx) drug abuse? [40]

Prescription drug abuse occurs when someone takes a drug in an improper way, for example:

- Without a prescription
- With a non-prescription
- Being induced to be "excited"

Every day 2,000 teenagers in the United States abuse Rx drugs for the first time.

- Rx drugs are the most commonly abused drugs by teenagers, second only to alcohol, marijuana and tobacco.

Commonly Abused Rx Drugs[41]

- Opioids-usually used to treat pain
- Stimulants-most commonly used to treat ADHD
- Central nervous system "CNS" sedatives-used to treat anxiety and sleep disorders.

Myth: Using stimulant drugs such as Adderall or Ritalin can help teenagers perform well in school by improving concentration and energy.

Stimulants [42]

Is particularly noteworthy for stimulants used to treat attention deficit hyperactivity didsorder. In 2004, patients diagnosed with poisoning due to non-medical use of amphetamine, dextroamphetamine or methylphenidate, underwent 7,873 emergency hospital admissions. The incidence rate in the 12 to 17-year-old age group is higher than that in the 18-year-old and older age group. More than two-thirds (68%) of the visits involved the non-medical use of these two drugs and another substance .

Sedatives and muscle relaxants [43,44]

Benzodiazepines are often diverted for non-medical purposes. They are commonly used as sleeping pills or anti-anxiety drugs. They can also be used to detoxify alcohol or other substances, and can be used to treat spastic diseases. Addicts use high doses of benzodiazepines to increase the euphoric effects of opioids; increase fascination with methadone or heroin; energetic cocaine; increase the effects of alcohol; or reduce withdrawal from heroin, methadone and The effects of other drugs. Relaxing muscles can also be compelling. Carisoprodol, a muscular relaxing acting relaxing sold centrally under the name of soma, is an example. Ingestion can cause addiction and a slight sense of euphoria.There is tolerance and there is an anxiety, tremor, muscle contraction syndrome, insomnia, hearing and visual hallucinations, and strange behavior.

Drugs for erectile dysfunction [45-52]

Sildenafil became the drug of Centinel erectile dysfunction in drug culture; There is an underground network of false recipes, foreign imports and Internet purchases. Both men and homosexual women and heterosexual women are documented to have demonstrated drug administration behavior with this substance. In a sexually active male

survey aged 18 to 25, 13% reported erectile dysfunction and 6% used drugs, but rarely under medical control and often mix With recreational drugs. Between men and homosexual women, the sildenafil, together with cocaine, glass metanfetamine, amile nitrate poppers, ecstasy, gamanahydroxibute, and ketamine has become a "drug drug". Effects. Recent Anecdotic Evidence suggests that Sildenafil abuse is becoming increasingly popular among Ecstasy's consumers to try to cancel the side effects of erectile dysfunction or drugs to improve the drug experience through the use of concomitant drugs for the Erectile dysfunction.

The Most Commonly Used Prescription Drugs are Divided Into Three Classes [53-55]

Opioids

Examples: Ossicodone (OxyContin), IDROCODONE (Vicodin) and Meridina (Demerol)
Medical Use: Opioids are used for pain or for Relieve cough treatment or diarrhea.
how they work: opioids are united to opioid receptors in the central nervous system & # 40; The brain and spinal cord & # 41;, avoiding the brain to receive pain messages.

Central Nervous System & # 40; CNS & # 41; Deprestors

Examples: phenobarbital (Luminal), diazepam (Valium), and alprazolam (Xanax)
Medical Uses: Snc Dressants are used to treat anxiety, tension, panic attacks and sleep disorders.
How to work: Deprentive Depreent Snc decreasing decreasing brain activity by increasing the activity of a neurotransmitter called Gaba. The result is a sleepy or relaxing effect.

Stimulants

For example: methylphenidate (Ritalin) and amphetamine/dexamphetamine (Adderall)
Medical use: Stimulants can be used to treat narcolepsy and hyperactivity.
How they work: Stimulants increase brain activity, thereby increasing alertness, alertness and energy.

What Is The Danger Of Drug Abuse? [56-58]

If someone abuses drugs, whether it is street drugs, he is more likely to commit a crime, become a victim of a crime, or have an accident. As with any drug abuse, taking prescription drugs for the wrong reasons can pose serious health risks.

Abuse of Opioids can cause vomiting, mood swings, decreased thinking ability, and even decreased respiratory function, coma or death.

The Abuse of Central Nervous System inhibitors is also risky. Stopping suddenly or reducing too quickly can cause seizures. Taking central nervous system depressants and otherdrugs, such as prescription pain relievers, some over-the-counter cold and allergy medicines, or alcohol can slow down a person's heartbeat and breathing—or even kill them.

Abuse of Stimulants can cause heart failure or seizures. When stimulants are mixed with other drugs, these risks increase—even over-the-counter drugs like cold medicines.

Abused OTC Drugs [59-64]

OTC drugs are easy to obtain and difficult to detect in routine drug tests. Once the main drugs of drug users are removed from OTC drugs and herbal medicines, they can be used as a substitute for DOC.

In a study of 511 men who participated in 5 gyms, it was found that 18% reported using androsteredione or other anabolic steroids to increase muscle mass; 25% used them Ephedrine acts as a stimulant.

The Most Commonly Misused Over-The-Counter Drugs [69,70]

The availability of over-the-counter (OTC) drugs provides a wealth of benefits to the public-but it also has drawbacks, including the possibility of abuse and addiction.

Compared with prescription drugs, OTC drugs are more readily available and generally affordable, and therefore are widely used to treat common diseases.

Oxybutynin Trans Dermal System [77,78]

Although it is an OTC, this medicine can only be used after consulting a doctor. Oxybutynin is used to treat overactive bladder in women with urge incontinence and urination/frequency ≥ 3 months. If abused, this anticholinergic drug will reduce symptoms of depression, euphoria and relaxation.

examples: Oxytrol (female) and Ditropan XL.

General side effects: drowsiness, dizziness, confusion, dry mouth, constipation and blurred vision is contraindicated in: patients younger than 18 years old, patients with urinary tract infection and patients with unexplained low back pain. Maximum dose: 20 mg/d oral immediate release; 30 mg/d oral Ditropan XL extended release.

Cyclizine [87]

Abuse of Cyclizine hydrochloride is an over-the-counter drug that occurs frequently in Utah. Cyclizine is an over-the-counter antihistamine.These patients accounted for 89% of the cyclizine intake. Hallucinations (70%) and confusion and disorientation (40%) are the most obvious symptoms. Tachycardia (52%) and systolic hypertension (69%) are common among patients who come to the hospital. There are no serious complications.

OTC Analgesics[88]

The use of high levels of OTC analgesics, including aspirin and acetaminophene, for long periods of time have been associated with the disopy mood states.The withdrawal of phenacetin from the market in the 1970s was intoxicating and dissociated.

Intravenous Epinephrine [89]

A case that demonstrates the lengths that people will take to convert OTC drugs into drug drugs of abuse, 19 year old man who injected intravenously 1.1 mg of epinephrine (adrenaline) which is It was removed from an OTC bronchodilator inhaler which is generally used for asthma.

Hypnotic OTC (OFF AIDS) [90]

Uses in excess, sleeping supports (Sominex, Nytol and sleep EZE) can cause hallucinations, delusions, and confusion. When use is stopped, recovery is faster and there is no withdrawal syndrome.

Doctors Strategy [91]

Physicians should be alert for prescription and abuse of over-the-counter medications.Strategies that can be used include: collection of information on prescription, over-the-counter, and the use of herbal medicines in the original test; To investigate the illegal use of drugs during visits; Provide removing containers that patients can use to dispose of their unused prescription and unnecessary or over-the-counter medications;

Literature Review Misuse Of Over The Counter Drugs And Prescription Drugs [92-124]

Drugs that patients receive for the treatment of common diseases without a doctor's prescription are called over-the-counter drugs or over-the-counter drugs. Over-the-counter drugs provide prevention and treatment for a variety of diseases, including but not limited to headaches, colds, musculoskeletal pain, allergies, tobacco addiction, and heartburn. However, there are always risks in using over-the-counter drugs. Wazaify M *et al.* Al OTC advertising is often the driving factor for patients to choose OTC drugs. If the advertisement is misleading, the patient may be misled. The advertisement focuses on the beneficial effects of the drug and only provides information on contraindications and safety issues. In this case, the pharmacist can also gain insight into all aspects of the drug and

information on how to use over-the-counter drugs safely. Mercola J *et al.* Al Pharmacists and their pharmacies face some challenges in monitoring OTC abuse. The lack of consistent data on OTC drugs can make it difficult to identify drug-related problems. Pharmacists generally do not keep records or monitor patient drug files for over-the-counter drug use, creating a vacuum in the information needed to make appropriate consultation decisions. Covington T *et al.* Prescription drugs, such as quetiapine, gabapentin, Zdrugs, bupropion, venlafaxine, and over-the-counter drugs, such as loperamide, dextromethorphan, bendamine, promethazine, chlorpheniramine, diphenhydramine, and Diphenhydramine has been misused or misused in the literature on drug users' online sites that report new drug abuse trends and experiments. Daniulaityte R *et al.* Al The most common risk of abuse of prescription drugs may be addiction.People who abuse drugs become addicted as quickly as drugs. This is one of the reasons why most doctors will update their prescriptions unless they see the patient-they want to check the patient to make sure he or she is not addicted. Romanelli F *et al.* Perform needs analysis (and risk assessment) Establish and maintain treatment relationships clarify service users and their drug-related goals Discuss, implement, evaluate and revise treatment plans to address client goals and needs with other care providers Contact and cooperation Boyd CJ *et al.*

CONCLUSION

The abuse of prescription drugs and OTC drugs has aroused increasing public interest worldwide. Current medication regimens pose major challenges for healthcare providers and pharmacists, especially during the COVID19 pandemic. It is recommended that these health professionals remain vigilant and develop strategies to ensure the continuity of care for drug users and people with drug problems, and to prevent possible drug abuse and diversion, provide clear information about the effects of drugs, and provide clear information on all possible drugs Interactions provide advice; promoting community maintenance programs and interrupted.The current health system requires strengthening the supervision of OTC drugs, especially those drugs that have been determined to be abused. Finally, data collection and reporting on OTC drug abuse can be standardized to clearly report drug abuse, abuse, and addiction.

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RESEARCH ARTICLE

Strong 2 – Domination in Intuitionistic Fuzzy Graph

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ABSTRACT

In this paper we introduce the concept of strong 2 domination of an Intuitionistic fuzzy graph. We determine the strong 2 – domination number $d(G)$ of the intuitionistic fuzzy graph G is the minimum cardinality taken over all strong 2 – dominating number of an Intuitionistic fuzzy graph and that of its complement are discussed. Also prove some results on strong 2 – dominating set.

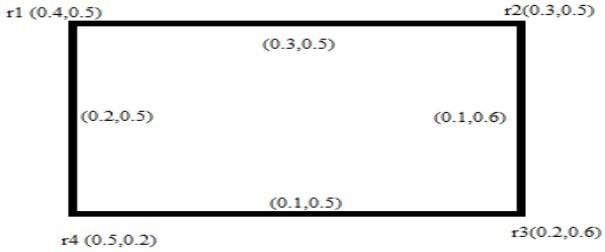
Keywords: Intuitionistic fuzzy graph, strong domination, 2-domination, strong 2-domination set, strong 2 – domination number.

INTRODUCTION

A. Rosefield introduced the notion of fuzzy graphs and studied fuzzy analogs of graph theoretic concepts such as paths, cycles and connectedness [6]. M.Chelllai and D. Favaron[1] introduced the independence and 2-domination in trees. A. Somasundaram and S. Somasundaram [9] discussed domination in fuzzy graphs. R. Parvathi and G. Thamizhendhi [5] discussed domination in Intuitionistic fuzzy graphs. R. Parvathi and M.G Karunambigai [3] gave a definition for Intuitionistic fuzzy graph as a special case of Intuitionistic fuzzy graphs defined by K.T Atonassov and A. Shannon [8]. In this paper we introduced dominating set, strong domination, 2- domination set, and domination number in Intuitionistic fuzzy graphs.

PRELIMINARIES

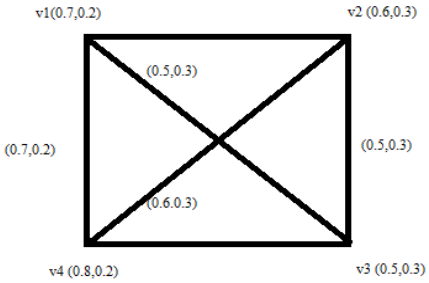
Definition 2.1
An Intuitionistic fuzzy graph is of the form $G = (V, E)$ where $V = \{a_1, a_2, \dots, a_n\}$ such that $\mu: v \to [0,1]$ and $\gamma: v \to [0,1]$ denote the degree of membership and non membership of the element $a_i \in V$ respectively and
$0 \leq \mu(a_i) + \gamma(a_i) \leq 1$ ----(1)



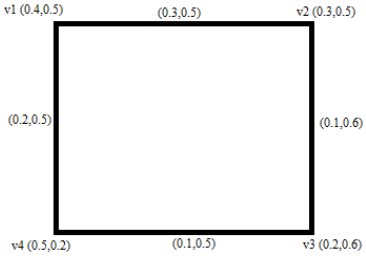
for every $a_i \in V$ $(i = 1,2,\dots,n)$
$E \subseteq V \times V$ where $\mu_1 : v \times v \rightarrow [0,1]$ and $\gamma_1 : v \times v \rightarrow [0,1]$are such that
$\mu_1(a_i,a_j) \leq \min[\mu(a_i),\mu(a_j)]$---------- 2
$\gamma_1(a_i,a_j) \leq \max[\gamma(a_i),\gamma(a_j)]$---------- 3
And $0 \leq \mu_1(a_i,a_j) + \gamma_1(a_i,a_j) \leq 1$---------- 4
for every $(a_i,a_j) \in E$

Definition 2.2
An Intuitionistic fuzzy graph $H = (V',E')$ is said to be an intutionistic fuzzy subgraph of the intuitionistic fuzzy graph $G = (V,E)$ if $V' \subseteq V$and$E' \subseteq E$.
Or equivalently if $\mu'_{1i} \leq \mu_{1i}$, $\gamma'_{1i} \geq \gamma_{1i}$ and $\mu'_{2j} \leq \mu_{2ij}$, $\gamma'_{2ij} \geq \gamma_{2ij}$ for every $i,j = 1,2,\dots.n$

Definition 2.3
An Intuitionistic fuzzy graph is complete if $\mu_{2ij} = \min(\mu_{1i},\mu_{1j})$ and $\gamma_{2ij} = \max(\gamma_{2i},\gamma_{2j}) \forall (a_i,a_j) \in V$.



Definition 2.4
Let $G = < V,E >$ be an intuitionistic fuzzy graph then the order of G is defined to be an Intuitionistic fuzzy graph then the order of G is defined to be $O(G) = (O_\mu(G),O_\gamma(G))$ where $O_\mu(G) = \sum_{a \in v} \mu_1(a)$ and $O_\gamma(G) = \sum_{a \in v} \gamma_1(a)$



$O(G) = (0.4 + 0.3 + 0.5 + 0.2, 0.5 + 0.5 + 0.6 + 0.2)$
$O(G) = (1.4,1.8)$

Definition 2.5

The size of G is defined to be $S(G) = S_\mu(G), S_\gamma(G)$ where $S_\mu(G) = \sum_{u \neq v} \mu_2(u,v)$ and $S_\gamma(G) = \sum_{u \neq v} \gamma_2(u,v)$

$$S(G) = (0.3 + 0.1 + 0.1 + 0.2\,, 0.5 + 0.6 + 0.5 + 0.5)$$

$$S(G) = (0.7, 2.1)$$

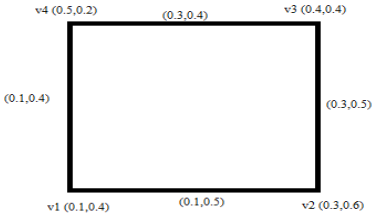
Definition 2.6

The complement of an Intuitionistic fuzzy graph $G = (V, E)$ is an Intutionistic fuzzy graph, $\bar{G} = (\bar{V}, \bar{E})$Where

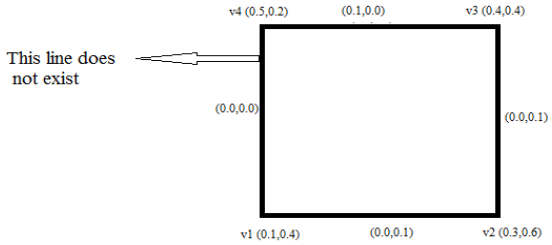
(i) $\bar{V} = V$

(ii) $\bar{\mu}_{1i} = \mu_{1i}$ and $\bar{\gamma}_{1i} = \gamma_{1i}\ \forall\ (i = 1,2,\dots,n)$

(iii) $\bar{\mu}_{2ij} = \min(\mu_{1i}, \mu_{ij}) - \mu_{2ij}$ and $\bar{\gamma}_{2ij} = \max(\gamma_{1i}, \gamma_{ij}) - \gamma_{2ij} \forall\ (i, j = 1,2,\dots,n)$



G



$\bar{G}$

Definition 2.7

A set D of nodes of G is strong domination set of G if every node $V(G) - D$ is a strong neighbor of some node in D.

Definition 2.8

The weight of a strong dominating set D is defined as $W(D) = \sum_{\mu \in D} \mu(a,b)$ where $\mu(a,b)$ is the membership values of the strong arcs incident on$u$. The strong domination number of the intutionistic fuzzy graph G is defined as the minimum weight of strong dominating sets of G and it is denoted by$d(G)$.

Definition 2.9

A subset D of V is called a 2-domination set on G if for every node $v \in V - D\exists$ atleast two strong neighbors in$D$.

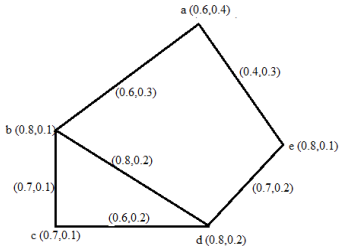
Definition 2.10

The 2 – domination number of an Intuitionistic fuzzy graph G denoted by $d_2(G)$, is the minimum cardinality of a 2 – dominating set of G.

STRONG 2-DOMINATION IN INTUITIONISTIC FUZZY GRAPH

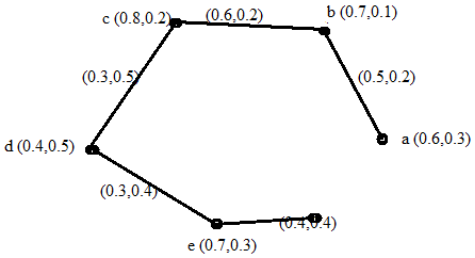
Definition 3.1

A set D of nodes of G is a strong dominating set and subset D of V is called 2-dominating set of G if for every node $v \in V - D$ is a two strong neighbor of some node in D is called strong 2-domination in the intuitionistic fuzzy graph.



Definition 3.2

The strong 2-domination number of a fuzzy graph G is defined as the minimum cardinality of a strong 2-dominating set of G. The strong 2-domination is denoted by $d_2(G)$ or d_2.



$\{b, e\}$ is strong 2-dominating set of the intuitionistic fuzzy graph G. $d_2 = 2$

Theorem 3.1

For any Intuitionistic fuzzy graph $G = (V, E)$, $d_2(G) + d_2(\bar{G}) < 2\,O(G)$, where $d_2(\bar{G})$ is the strong 2-domination number of $\bar{G}$ and equality holds iff $0 < \mu(a_i, a_j) < \bar{\mu}(a_i, a_j)$ and $0 < \gamma(a_i, a_j) < \bar{\gamma}(a_i, a_j)\ \forall\ a_i, a_j \in V$

Proof:

Since $d_2(G) = O(G)$ iff $\mu(a_i, a_j) < \bar{\mu}(a_i, a_j)$ and $\gamma(a_i, a_j) < \bar{\gamma}(a_i, a_j) \forall\ a_i, a_j \in V d_2(\bar{G}) = 2\,O(G)$ iff $\mu(a_i, a_j) - \mu(a_i, a_j) < \bar{\mu}(a_i, a_j)$ and $\gamma(a_i, a_j) - \gamma(a_i, a_j) < \bar{\gamma}(a_i, a_j)\ \forall a_i, a_j \in V$ which gives $\mu(a_i, a_j) > 0$ and $\gamma(a_i, a_j) > 0$.

Hence $d_2(G) + d_2(\bar{G}) < 2\,O(G)$

Theorem 3.2

Every non trivial connected Intuitionistic fuzzy graph G has strong 2-dominating set D whose complement $V - D$ is also a strong 2-dominating set.

Proof

Let G be a strong 2-dominating graph. Strong 2-dominating set of G is

$D - \{s\}$ ------- (1)

Let $\bar{G}$ be a strong 2-dominating graph. Strong 2-dominating set of $\bar{G}$is

$D - \{s\}$ ---------- (2)

From the equations 1 and 2,

Every non trivial connected Intuitionistic fuzzy graph G has a strong 2- dominating set D whose complement $V - D$ is also a strong 2- dominating set.

Hence the proof

Theorem 3.3

Let G be a fuzzy graph without isolated nodes. If D is a minimal strong 2- dominating set, then $V - D$ is strong 2-dominating set.

Proof:

Let 'a' be any bode in D. Since G has no isolated vertices, there is a node $e \in N(a)$.

There is a vertex or node $e \in V - D$. Thus, every element of D is strong 2 – dominated by element $V - D$

Hence the proof

Theorem 3.4

For any Intuitionistic fuzzy graph $G = (v, t)$ without isolated nodes $d_2(G) \leq \frac{O(G)}{2}$

Proof:

Let D be a minimal strong 2- domination set of G. Then $V - D$ is a strong 2- dominating set of G.

Therefore
$d_2(G) + d_2(G) \leq 2\,O(G)$
$2\,d_2(G) \leq O(G)$
$d_2(G) \leq \frac{O(G)}{2}$
Hence the proof

Note 1:

Let G be an intuitionistic fuzzy graph such that both G and $\bar{G}$ have no isolated nodes, then $d_2(G) + d_2(\bar{G}) \leq O(G)$ equality holds iff

$$d_2(G) = d_2(\bar{G}) = \frac{O(G)}{2}$$

Theorem 3.5

Every strong 2- dominating set of an Intuitionistic fuzzy graph G is domination set of G.

Proof:

Let D be a strong 2- dominating set of the Intuitionistic fuzzy graph G. Then every node $V - D$ has two strong neighbors in D.
(i.e.)for every node $e \in V - D$ there exist minimum two nodes in D and both dominates e.
Every node in $V - D$ is dominated by strong two nodes in D. Thus D is a dominating set of G.

Note 2:

If G is an Intuitionistic fuzzy graph then $d_2(G) > d(G)$

CONCLUSION

The concept of domination in graph is very rich both in theoretical development and applications. In this paper the concept of strong 2- domination has been modified for Intuitionistic fuzzy graphs. We defined strong 2- domination set and strong 2- domination number in Intuitionistic fuzzy graph. Further we proved the theorems based on strong 2- domination of Intuitionistic fuzzy graph.

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RESEARCH ARTICLE

The GC MS Study of One Ayurvedic Formulation, Pushyanuga Churnam

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ABSTRACT

The present study deals with the GC MS analysisof one Ayurvedic medicine, Pushyanugachuram which is prescribed for Menorrhagia, Metrorrhagia, Leucorrhoea, Haemorrhoids, and Menstrual disorders. The medicine was procured from standard Ayurvedic vendor and subjected to GC MS analysis after processing it by standard protocol. The GC MS profile indicated the presence of 38 compounds among which some molecules such as beta.-curcumene, .beta.-Bisabolene, .alpha.-acorenol, 2-Naphthalenemethanol, decahydro-.alpha.,.alpha.,4a-trimethyl-8-methylene-, [2R-(2.alpha., 4a.alpha., 8a.beta.)]-, .alpha.-Bisabolol, 1,3,3-Trimethyl-2-(2-methyl-cyclopropyl)-cyclohexene, 11,14-Octadecadienoic acid, methyl ester, Methyl stearate, E,E,Z-1,3,12-Nonadecatriene-5,14-diol, Squalene,

Stigmasterol, .gamma.-Sitosterol, .beta.-Amyrin etc. indicated promising medicinal roles. There is enough evidence to prove the medicinal role of Phushyanugachurnam in ameliorating some gynaecological diseases as found from the medicinal roles of the molecules present therein.

Keywords: Pushyanugachurnam, GC MS, Ayurvedic, beta.-curcumene, .beta.-Bisabolene, .alpha.-acorenol.

INTRODUCTION

Modern scientific testing of Ayurvedic and other forms of alternative medicines are required to understand the mechanism of action of these medicines. After the advent of Corona disease, this has become all the more pertinent since the world is looking for new formulations and strategies. There are some reports on the standardization of Ayurvedic and Sidhha medicines but it is a long way to go in this regard.[1-29]The present study deals with the GC MS analysis of one Ayurvedic formulation, Pushyanuga Churnam, which is prescribed to treat excessive bleeding disorders such as Menorrhagia, Metrorrhagia, Leucorrhoea, Haemorrhoidsa and Menstrual disorder. Pushyanuga Churnamshould be administered under strict medical supervision. This medicine is made of a number of plant parts as mentioned below: Patha (*Cyclea peltata*), Jambubeejamajja (*Eugenia jambolana*), Amrabeejamajja (*Mangifera indica*), Shilabheda or Pasanabheda (*Aerua lanata*), Rasanjana (*Berberis aristata*), Ambasthaki (*Cissampelos pereira*), Mocharasa or Shalmaliniryasa (*Salmalia malabarica* exudate), Samanga or Lajjalu (*Mimosa pudica*), Padma kesara or Kamala (*Nelumbonuceifra*), VahlikaotKumkuma (*Crocus sativus*), Ativisha (*Aconiyum heterophyllum*), Musta (*Cyperus rotundus*), Bilva (*Aegle marmelos*), Lodhra (*Simplocos racemosa*), Gairika (red ochre), Katphala (*Myricanagi*), Maricha (*Piper nigrum*), Sunthi (*Zingiber officinalis*), Draksha or Raisins (*Vitis vinifera*), Raktachandana (*Pterocarpus santalinus*), Katvanga or Araluka (*Oroxylum indicum*), Kutaja or Vatsaka (*Holarrhena antidysentrica*), Anantha or Swathasariva (*Hemidesmus indicus*), Dhataki (*Woordfordia fruticosa*), Madhuka or Yastimadhu or Licorice (*Glycyrriza glabra*) and Arjuna (*Terminalia arjuna*). All the above ingredients are dried and powdered in mixed in equal quantity to make this medicine. The dosage of this medicine is 1-3 g in honey once or twice a day as per Physician's advice. This medicine is made according to the Ayurvedic treatise CharakaSamhita, Chikitsasthana, 30/90-96 and Bhaishjyaratnavali, Streerogadhikara: 46-49, Ashtangahridayam. The manufacturers of this medicine are AVN, Baidyanath, Vaidyaratnam and Nagarjuna among others.

MATERIALS AND METHODS

Pushyanuga Churnam was obtained from standard Ayurvedic vendor at Chennai and was subjected to GC MS analysis by standard procedure.

Instrument

Gas chromatography (Agilent: GC: (G3440A) 7890A. MS MS: 7000 Triple Quad GCMS,) was equipped with Mass spectrometry detector.

Sample Preparation

100 micro lit sample Dissolved in 1 ml of suitable solvents. The solution stirred vigorously using vortex stirrer for 10 seconds. The clear extract was determined using gas-chromatography for analysis.

GC-MS protocol

The GC MS Column consisted of DB5 MS (30mm×0.25mm ID ×0.25 μm , composed of 5% phenyl 95% methyl poly siloxane), Electron impact mode at 70 eV; Helium (99.999%) was used as carrier gas at a Constant flow of 1ml/min Injector temperature 280 °C; Auxilary Temperature : 290°C Ion-source temperature 280 °C. The oven Temperature was programmed from 50 °C (isothermal for 1.0 min), with an increase of 40°C/min, to 170°C C (isothermal for 4.0 min), then 10°C/min to 310°C (isothermal for 10min) fragments from 45 to 450 Da. Total GC running time is 32.02 min. The compounds are identified by GC-MS Library (NIST & WILEY).

RESULTS AND DISCUSSION

The GC MS profile of Pushyanuga Churnam is represented in Figure 1. Table1 indicates the retentions values, types of possible compound, their molecular formulae, molecular mass, peak area and their medicinal roles of each compound as shown in the GC MS profile of Pushyanuga Churnam. The identification of metabolites was accomplished by comparison of retention time and fragmentation pattern with mass spectra in the NIST spectral library stored in the computer software (version 1.10 beta, Shimadzu) of the GC-MS along with the possible pharmaceutical roles of each bio molecule as per Dr. Duke's Phytochemical and ethnobotanical data base (National Agriculture Library, USA) and others as shown in Table 1 [30]. It is heartening that some work on the authenticity of this medicine has been reported. Salve and Ghule, 2019 have reviewed the effect of Pushyanugachurnam on white discharge problem in patients.[31]Kumari*et al*, 2019 and Bhuvaneswari and Seetarama, 2017 have also studied the role of this medicine.[32,33]Tambekar and Dahikar, 2010 have studied the antibacterial roles of some ayurvedic medicines including PushyanugaChurnam.[34]Shailajan*et al,* 2017 have done marker based chemo-profiling of PushyanugaChurna.[35] In the present study the roles of some molecules such as .beta.-curcumene, .beta.-Bisabolene, .alpha.-acorenol, 2-Naphthalenemethanol, decahydro-.alpha.,.alpha.,4a-trimethyl-8-methylene-, [2R-(2.alpha.,4a.alpha.,8a.beta.)]-, .alpha.-Bisabolol, 1,3,3-Trimethyl-2-(2-methyl-cyclopropyl)-cyclohexene, 11,14-Octadecadienoic acid, methyl ester, Methyl stearate, E,E,Z-1,3,12-Nonadecatriene-5,14-diol, Squalene, Stigmasterol, .gamma.-Sitosterol, .beta.-Amyrin etc. have direct or indirect role on the hormonal balancing which could help cure the ailments. Some of the molecules, whose medicinal roles are not known, need further investigation.

CONCLUSION

From the results and discussion it is clear that Pushyanugachurnam is a potent medicine for some of the gynaecological diseases.

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Table 1. Indicates the retentions time, types of possible compound, their molecular formulae, molecular mass, percentage peak area and their medicinal roles of each compound as shown in the GC MS profile of Pushyanuga Churnam

Sl. No	Retention Time	Compound Name	Mol. Formula	Mol. Weight	% Peak Area	Possible medical Role
1	6.53	Coumarin, 3,4-dihydro-4,4,7-trimethyl-	C12H14O2	190.1	0.57	Not known
2	8.59	Bicyclo[5.2.0]nonane, 2-methylene-4,8,8-trimethyl-4-vinyl-	C15H24	204.2	1.13	Not known
3	9.40	Benzene, 1-(1,5-dimethyl-4-hexenyl)-4-methyl-	C15H22	202.2	1.24	Not known
4	9.56	.beta.-curcumene	C15H24	204.2	0.72	17 beta hydroxysteroid dehydrogenase inhibitor, Antiamyloid beta, Anto TGF beta, Beta receptor agonist, Beta-adrenergic receptor blocker, beta blocker, beta galactosidase inhibitor, beta glucuronidase inhibitor, ER beta binder

5	9.69	2-Azido-2,4,4,6,6,8,8-heptamethylnonane	C16H33N3	267.3	0.56	Not known
6	9.73	.beta.-Bisabolene	C15H24	204.2	1.14	17 beta hydroxysteroid dehydrogenase inhibitor, Antiamyloid beta, Anto TGF beta, Beta receptor agonist, Beta-adrenergic receptor blocker, beta blocker, beta galactosidase inhibitor, beta glucuronidase inhibitor, ER beta binder
7	9.89	Cyclohexene, 3-(1,5-dimethyl-4-hexenyl)-6-methylene-, [S-(R*,S*)]-	C15H24	204.2	0.73	Not known
8	11.02	.alpha.-acorenol	C15H26O	222.2	0.94	5, alpha-reductase inhibitor, alpha-amylase inhibitor, alpha-glucosidase inhibitor, alpha-reductase inhibitor, HIF 1 alpha inhibitor, increases alpha-N-mannosidase activity, interleukin-1 alpha inhibitor, testosterone 5-alpha reductase inhibitor TNF-alpha inhibitor
9	11.23	2-Naphthalenemethanol, decahydro-.alpha.,.alpha.,4a-trimethyl-8-methylene-, [2R-(2.alpha.,4a.alpha.,8a.beta.)]-	C15H26O	222.2	4.64	5, alpha-reductase inhibitor, alpha-amylase inhibitor, alpha-glucosidase inhibitor, alpha-reductase inhibitor, HIF 1 alpha inhibitor, increases alpha-N-mannosidase activity, interleukin-1 alpha inhibitor, testosterone 5-alpha reductase inhibitor TNF-alpha inhibitor
10	11.28	2-Naphthalenemethanol, 1,2,3,4,4a,5,6,8a-octahydro-.alpha.,.alpha.,4a,8-tetramethyl-, [2R-(2.alpha.,4a.alpha.,8a.beta.)]-	C15H26O	222.2	0.83	Not known
11	11.68	.alpha.-Bisabolol	C15H26O	222.2	1.54	5, alpha-reductase inhibitor, alpha-amylase inhibitor, alpha-glucosidase

						inhibitor, alpha-reductase inhibitor, HIF 1 alpha inhibitor, increase alpha-N-mannosidase activity, interleukin-1 alpha inhibitor, testosterone 5-alpha reductase inhibitor TNF-alpha inhibitor
12	13.58	Tricyclo[4.4.0.0(2,7)]dec-8-ene-3-methanol, .alpha.,.alpha.,6,8-tetramethyl-, stereoisomer	C15H24O	220.2	10.22	Not known
13	13.65	13-Oxadispiro[5.0.5.1]tridecane	C12H20O	180.2	2.39	Not known
14	13.78	2-Propen-1-ol, 3-(2,6,6-trimethyl-1-cyclohexen-1-yl)-	C12H20O	180.2	1.09	Not known
15	14.19	Naphthalene, decahydro-1,1-dimethyl-	C12H22	166.2	9.66	Not known
16	14.34	1,3,3-Trimethyl-2-(2-methyl-cyclopropyl)-cyclohexene	C13H22	178.2	1.31	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor
17	14.57	Estra-1,3,5(10)-trien-17.beta.-ol	C18H24O	256.2	2.23	Not known
18	15.73	11,14-Octadecadienoic acid, methyl ester	C19H34O2	294.3	4.95	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
19	15.80	9-Octadecenoic acid, methyl ester, (E)-	C19H36O2	296.3	10.19	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
20	16.06	Methyl stearate	C19H38O2	298.3	2.42	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor

21	16.17	Oleic Acid	C18H34O2	282.3	3.73	Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
22	17.70	4-Butylbenzoic acid, 1-adamantylmethyl ester	C22H30O2	326.2	10.36	Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
23	18.52	2,3-Dihydroxypropyl elaidate	C21H40O4	356.3	0.61	Not known
24	18.83	9,12-Octadecadienoic acid (Z,Z)-	C18H32O2	280.2	1.16	Acidifier, Arachidonic acid inhibitor, Increase Aromatic Amino acid Decarboxylase activity
25	18.88	9,12,15-Octadecatrienoic acid, 2,3-dihydroxypropyl ester, (Z,Z,Z)-	C21H36O4	352.3	2.94	Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
26	19.10	Hexadecanedioic acid	C16H30O4	286.2	1.74	Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
27	19.41	Bis(2-ethylhexyl) phthalate	C24H38O4	390.3	4.78	Not known
28	20.44	E,E,Z-1,3,12-Nonadecatriene-5,14-diol	C19H34O2	294.3	1.83	Anticancer, Cytochrome P450-2E1 inhibitor, Decreases C-telopeptide excretion, DecreasesDeoxypyridinoline excretion, Decreases endothelial leukocyte adhesion, Decreases endothelial platelet adhesion, Decreases epinephrine production, Decrease oxalate excretion
29	21.33	Decanedioic acid, bis(2-ethylhexyl) ester	C26H50O4	426.4	2.31	Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
30	21.47	Squalene	C30H50	410.4	1.06	Monooxygenase inhibitor, biochemical precursor in the preparation of steroids, natural moisturizer, used in cosmetics
31	23.82	2-[4-methyl-6-(2,6,6-trimethylcyclohex-1-enyl)hexa-1,3,5-	C23H32O	324.2	0.57	Not known

		trienyl]cyclohex-1-en-1-carboxaldehyde				
32	24.03	Stigmasterol	C29H48O	412.4	2.01	Precursor of progesterone , acts as intermediate in the biosynthesis of androgens and estrogens, anti-osteoarthritic, antihypercholesterolemic, cytotoxic, antitumor, hypoglycemic, antimutagenic, antioxidant, anti-inflammatory, analgesic.[36]
33	24.38	.gamma.-Sitosterol	C29H50O	414.4	2.85	PPAR-gamma antagonist
34	24.49	.beta.-Amyrin	C30H50O	426.4	0.55	17 beta hydroxysteroid dehydrogenase inhibitor, Antiamyloid beta, Anto TGF beta, Beta receptor agonist, Betaadrenergic receptor blocker, beta blocker, beta galactosidase inhibitor, beta glucuronidase inhibitor, ER beta binder
35	25.14	.alpha.-Amyrin	C30H50O	426.4	0.55	5 alpha reductase inhibitor, alpha amylase inhibitor, alpha glucosidase inhibitor, Antibacterial, Antioxidant, Potential antiplatelet,Hypoglycemic, Hypolipidemic, Sedative,Hepatoprotective
36	25.19	Fenretinide	C26H33NO2	391.3	1.19	Not known
37	25.40	Lup-20(29)-en-3-ol, acetate, (3.beta.)-	C32H52O2	468.4	1.90	Not known
38	26.23	1,2-Benzenediol, 3,5-bis(1,1-dimethylethyl)-	C14H22O2	222.2	0.69	Not known

Qualitative Compound Report

Data File	200520014.D	**Sample Name**	Pushyanuga Churnam
Sample Type		**Position**	26
Acq Method	GC Screening Method.M	**Acquired Time**	22-05-2020 AM 05:14:29
Comment			

User Chromatogram

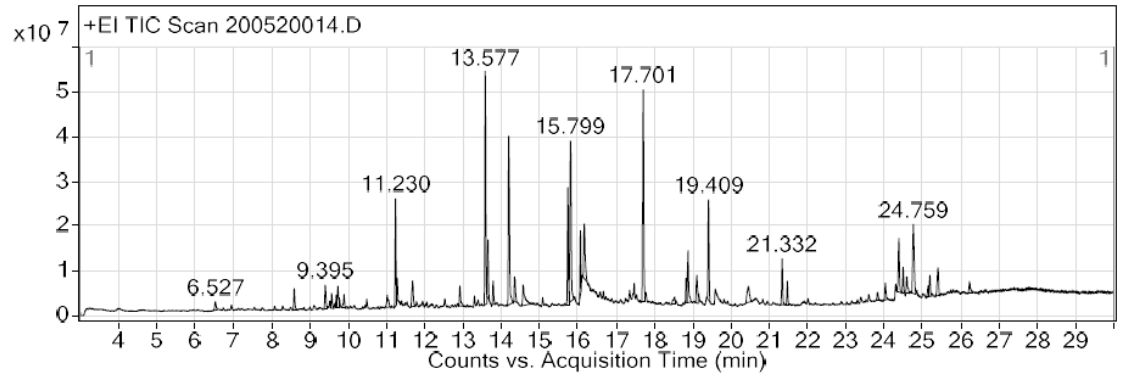

Figure 1. Depicts the GC MS profile of PushyanugaChurnma

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RESEARCH ARTICLE

Evaluation of Antibacterial and Antifungal Activity of Methanolic Extracts of Stem-Bark of the Selected Plants

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ABSTRACT

Plants have been used as rich sources of natural therapeutic agents to cure various illnesses. Due to increasing resistance to traditional antibiotic drugs, demand for discovery of safer antimicrobial agents has been increased. Due to presence of different phytochemicals, plant extracts show antimicrobial activity. In the present investigation, methanolic extracts of stem-bark of the selected trees (*Holoptelia integrifolia, Pscidium guajava, Pongamia pinnata, Syzygium cumini, and Bombax cieba*) were evaluated for their antibacterial (*E. coli*, and *S. aureus*), and antifungal (*A. niger*, and *P. chrysogenum*) at different concentrations (30 mg/L, 60 mg/L, 90 mg/L) along with standard antibiotic drug as positive control by well diffusion method. Results showed the presence of good antimicrobial activity of all the extracts. For *E. coli*, maximum MIC was observed by extract of *P. pinnata* (75-80 mg/L) and *B. cieba* with the lowest MIC values (15-20 mg/L) while *P. guajava* and *P. pinnata* extracts were found to have more potential against *S. aureus* (MIC- 15-20 mg/L). Extract of *H. integrifolia*, *S. cumini*, and *B. cieba* were equally effective against *A. niger* (MIC 15-20 mg/L) while the lowest MIC value against *P. chrysogenum* was shown by extract of *H. integrifolia.* Results of the present study concluded that the stem-bark of selected trees have active compounds which are responsible for their antimicrobial activity. Further, identification, and isolation of those active compounds may pave path for pharmaceutical industries to formulate new antimicrobial drugs.

Keywords: antibacterial, antifungal, phytochemicals, stem bark, MIC etc.

INTRODUCTION

An increase in microbial resistance to antimicrobial agents has been worldwide during past decades (Livermore, D.M., 1995; Jones, R.N. *et al*., 1997; Kolar, M. *et al*., 2001). The development of new antimicrobial compounds against different microorganisms is becoming critically important, as infectious diseases are still one of the leading causes of death in the world. The pharmaceutical industry is searching for new lead compounds with novel chemical structures to overcome the increasing resistance to known antibiotics. Green plants represent a useful source of reservoir of effective chemotherapeutics and can provide valuable source of natural antimicrobials (Balandrin, M.F. *et al*., 1985; Satish, S. *et al*., 1999). Antimicrobials of plant origin are effective in the treatment of infectious diseases while fewer side effects often associated with natural products as compared to synthetic antimicrobials (Kokosha, L. *et al.,* 2002). Studies show that waste material such as stembark can be used successfully as a major source of phytochemicals and antioxidants. Studies have revealed the presence of a wide range of secondary metabolites, including flavonoids, triterpenoid, saponins, and phenolic acids in gourd vegetables possessing distinct biological activities (Rizvi, M.M.A., 2009). Throughout the world, plant-based medicines are used traditionally to treat many ailments, particularly infectious diseases, such as diarrhoea, fever, cold as well as for the purpose of birth control and dental hygiene (Mitscher, *et al*., 1987). In India, thousands of species of plants are known to have medicinal value and the use of different parts of several medicinal plants to cure specific ailments has been invogue since ancient times. Ayurveda or Ayurvedic medicine is a system of traditional medicine, which is native to India (Chopra and Ananda, 2003) and form an alternative system of medicine. In the present investigation, stem bark of the selected plants (*Holoptelia integrifolia, Pscidium guajava, Pongamia pinnata, Syzygium cumini, and Bombax cieba*) were evaluated for their antibacterial and antifungal activity.

MATERIALS AND METHODS

Collection of plants and extract preparation

Stem bark of the selected trees (*Holoptelia integrifolia, Pscidium guajava, Pongamia pinnata, Syzygium cumini, and Bombax cieba*) were collected from campus of University of Rajasthan, Jaipur, Rajasthan. Those were taken to the laboratory to be washed and dried in air at room temperature. For determination of moisture content, all the collected samples were kept in a flat-bottom dish in an air oven at 105°C for 1,3,5 hours and allowed to cool at room temperature in a desiccator and then weighed. The procedure was repeated until successive weighing agrees to as constant weighing. The loss in weight of the plant material was regarded as a measure of moisture content. The air-dried and coarsely powered, approximately 30 g of plant samples were places in Soxhlet extractor with 150 ml methanol for 24 h. Then, these were filtered using Whatman filter paper No. 1. The extracts were then concentrated to dryness under reduced pressure and controlled temperature by a rotary evaporator. The obtained extracts were dried over anhydrous $CaCl_2$ and utilized for further evaluation.

Antimicrobial analysis

Dried plant extracts were used for evaluate their antimicrobial activity. These were investigated by using well diffusion assay method. For this, 2 bacterial and 2 fungal strains were used to investigate antimicrobial activities. Pure cultures of bacterial isolates of *Staphylococcus aureus* MTCC 87, *Escherichia coli* MTCC 1652, and pure culture of fungal isolates *viz. Aspergillus niger* NCIM (National Collection of Industrial Microorganisms, Pune) 0616, *Penicillium chrysogenum* MTCC 2725, were collected from Department of Botany, University of Rajasthan, Jaipur, India, which were used as indicator organisms. The fungal cultures were sub-cultured on sterile Potato Dextrose Agar (PDA) and incubated at 28^{o}C for 48 hrs. The bacteria were grown in Nutrient Agar (NA) medium (prepared by autoclaving 8% Nutrient agar in distilled water at 15 lbs psi for 25-30 min) and incubating at 37^{o}C for 48 hrs. All fungal and bacterial cultures were further maintained on the same medium after every 48 hrs. Fresh suspensions of test organisms in saline solution were prepared from freshly grown agar slants before every antimicrobial assay.

Antibacterial Assay: Standard microbial technique- The Agar Well Diffusion method (Perez, C. *et al*., 1990) was used for *in-vitro* antibacterial assay. The different samples were diluted by using 10% di-methyl sulphoxide (DMSO) and 3 different concentrations (30 mg/L, 60 mg/L, and 90 mg/L) of all extracts were prepared. Disinfected Petri dishes holding the nutrient agar (NA) medium were inoculated with the microorganisms under investigation with spreader and allowed to stand for 30 min. Wells of 6mm diameter were prepared in the seeded agar plates. With equal distance control well was also prepared. All different concentrations of all the samples and standard drug (30µl) poured into the preorganized wells of seeded plates. The plates were incubated at 37ºC for 24 hrs. The antibacterial spectrum of the test sample was determined in terms of inhibition zone (IZ) around each well. The diameters of inhibition zone produced by the test sample were compared with the inhibition zone, produced by the commercial control antibiotics ciprofloxacin (1mg/ml).

Antifungal Assay: Antifungal activity was screened by modified agar well diffusion method (Bonjar, G.H.S., 2004). Petri plates having PDA medium were inoculated with the fungal strains (7 days old) separately suspended in saline solution. The plates were dried out at room temperature for 15 min. Wells of 6 mm in diameter were perforated on the agar using cork-borers. With equal distance control well was also prepared. The different samples were diluted by using 10% di-methyl sulphoxide (DMSO) and 3 different concentrations (30 mg/L, 60 mg/L, and 90 mg/L) of all the extracts, were also prepared. All different concentrations of all samples and standard drug seeded into the wells of preorganized Patri plates. Seeded plates were incubated at 28°C for the 48 hours. After incubation, antifungal activities were determined by computing the diameter of IZ (mm). All experimentations were made thrice and mean values were calculated. Ketokenazole (1mg/ml) was used as the standard control for antifungal assay.

Determination of Activity Index (AI)

The activity index (AI) for all the plant extracts were calculated as:

$$\text{Activity index (A.I.)} = \frac{\text{Mean of inhibition zone of the extract}}{\text{inhibition zone obtained for standard antibiotic drug}}$$

Determination of Minimum Inhibitory Concentration (MIC)

The Macro-broth dilution technique was used to determine minimum inhibitory concentration of the extracts by diluting a given volume of the extract to various concentrations (Baron, E.J. *et al*., 1990). Wells were made on the agar surface with a sterile cork borer (6mm) and the wells were appropriately labelled. The different concentrations were used to fill up the wells using Pasteur pipette. This was followed by the incubation of the plates at 37^{0}C for 24 hours for bacteria and 28^{0}C for 48 hours for fungi. The minimum dilution of sample that inhibits the growth of the organism was taken as Minimum Inhibitory Concentration (Mathur, A. *et al*., 2011).

RESULTS AND DISCUSSION

Due to increasing resistance to traditional antibiotic drugs, need of natural antimicrobial agents with no side effects has been increased in recent years. Many plants have been identified as rich sources of therapeutic agents against various infectious diseases (Garcia-Olmedo, F. *et al*., 1998). In the present investigation, methanolic extracts of stem bark of the selected trees were found to possess inhibitory activity against the selected bacterial and fungal strains (Table 1).For *E. coli*, the maximum MIC was observed by extract of *P. pinnata* (75-80 mg/L) and *B. cieba* with the lowest MIC values (15-20 mg/L) (Figure 1) while *P. guajava* and *P. pinnata* extracts were found to have more potential against *S. aureus* (MIC- 15-20 mg/L) (Figure 2) and *H. integrifolia* with the maximum MIC values (50-55 mg/L). Extract of *H. integrifolia*, *S. cumini*, and *B. cieba* were equally effective against *A. niger* (MIC 15-20 mg/L) (Figure 3) and *P. guajava* and *P. pinnata* with the maximum MIC values (20-25 mg/L). Extract of *P. pinnata* has the maximum MIC value (45-50 mg/L) while the lowest MIC value against *P. chrysogenum* was shown by extract of *H. integrifolia*.

The antimicrobial activity of plant extracts is due to presence of various phytochemicals including secondary metabolites. Several researchers investigated the efficiency of plant extracts and their effective compounds as antimicrobial agents to control growth of food borne and spoilage bacteria. Some researchers have suggested that antimicrobial components of the plant extracts (terpenoid, alkaloid and phenolic compounds) interact with enzymes and proteins of the microbial cell membrane causing its disruption to disperse a flux of protons towards cell exterior which induces cell death or may inhibit enzymes necessary for amino acids biosynthesis (Burt, S., 2004). In our previous study, many important primary and secondary metabolites were found to be present in the selected plant parts (Jonwal, R. *et al*., 2021). The inhibitory effect of these plant extracts to hydrophobicity characters of these plants extracts which enable them to react with protein of microbial cell membrane and mitochondria disturbing their structures and changing their permeability (Friedman, *et al*., 2004, Tiwari, *et al*., 2009). The present study suggested that plant parts, which are not considered useful, can be used as natural source of antimicrobial agents.

CONCLUSION

Results of the present investigation concluded that stem bark of the selected trees are good sources of natural antibacterial and antifungal agents. So, further identification, and isolation of responsible phytochemicals may help pharmaceutical industries to formulate new drugs against various infectious diseases.

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Table 1: Antimicrobial activity of methanolic extracts of stem-bark of the selected plants.

Name of the plant	S	30 mg/L		60 mg/L		90 mg/L		MIC (mg/L)
E. coli	**IZ**	**IZ**	**AI**	**IZ**	**AI**	**IZ**	**AI**	
Holoptelia integrifolia	51	11	0.21	15	0.29	18	0.35	20-25
Pscidium guajava	41	NA	NA	12	0.29	15	0.36	50-55
Pongamia pinnata	42	NA	NA	NA	NA	11	0.26	75-80
Syzygium cumini	41	NA	NA	NA	NA	13	0.31	70-75
Bombax cieba	40	11	0.27	12	0.30	14	0.35	15-20
S. aureus								
Holoptelia integrifolia	51	NA	NA	11	0.21	13	0.25	50-55
Pscidium guajava	48	9	0.18	12	0.25	15	0.31	15-20
Pongamia pinnata	47	9	0.19	11	0.23	13	0.27	15-20
Syzygium cumini	52	15	0.28	18	0.34	21	0.40	20-25
Bombax cieba	47	10	0.21	12	0.25	15	0.31	20-25
A. niger								
Holoptelia integrifolia	31	18	0.58	23	0.74	28	0.90	15-20
Pscidium guajava	29	11	0.37	17	0.58	20	0.68	20-25
Pongamia pinnata	26	14	0.53	21	0.80	25	0.96	20-25
Syzygium cumini	28	15	0.53	18	0.64	24	0.85	15-20
Bombax cieba	32	14	0.43	21	0.65	23	0.71	15-20
P. chrysogenum								
Holoptelia integrifolia	32	9	0.28	10	0.31	13	0.41	15-20
Pscidium guajava	25	12	0.48	18	0.72	21	0.84	20-25
Pongamia pinnata	24	NA	NA	11	0.45	13	0.54	45-50
Syzygium cumini	27	10	0.37	13	0.48	16	0.59	25-30
Bombax cieba	24	9	0.37	11	0.45	14	0.58	25-30

Note: IZ- Inhibition Zone (mm), AI- Activity Index, MIC- Minimum Inhibitory Concentration (mg/L), S- Standard antimicrobial drug (positive control), NA- No Activity.

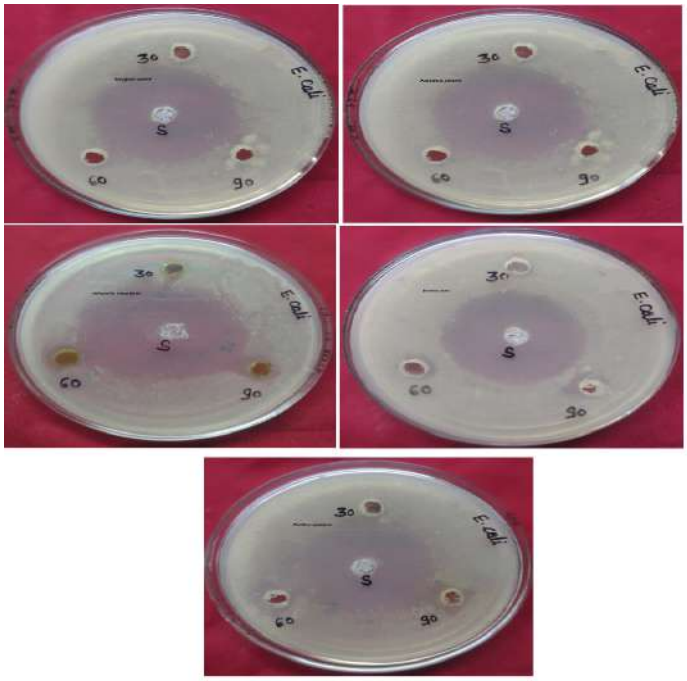

Figure 1: Antibacterial activity of methanolic extracts of stem bark of the selected plants against *E. coli*.

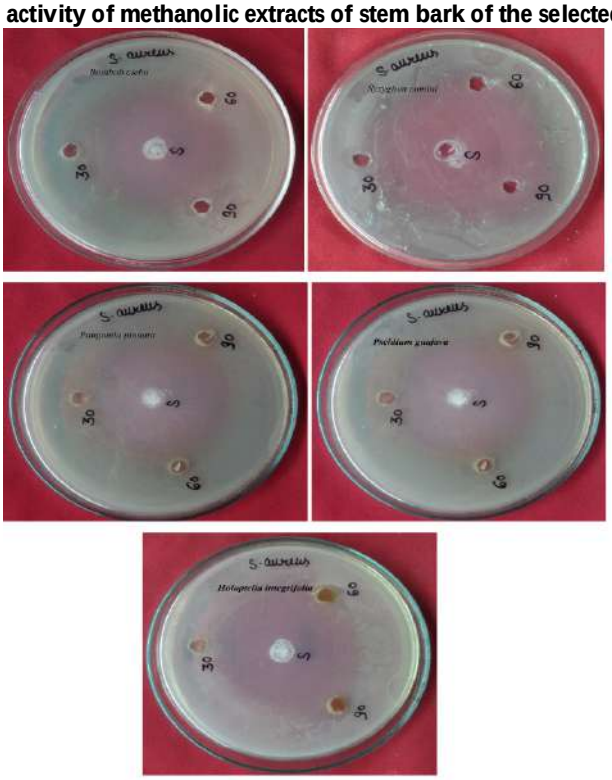

Figure 2: Antibacterial activity of methanolic extracts of stem bark of the selected plants against *S. aureus*.

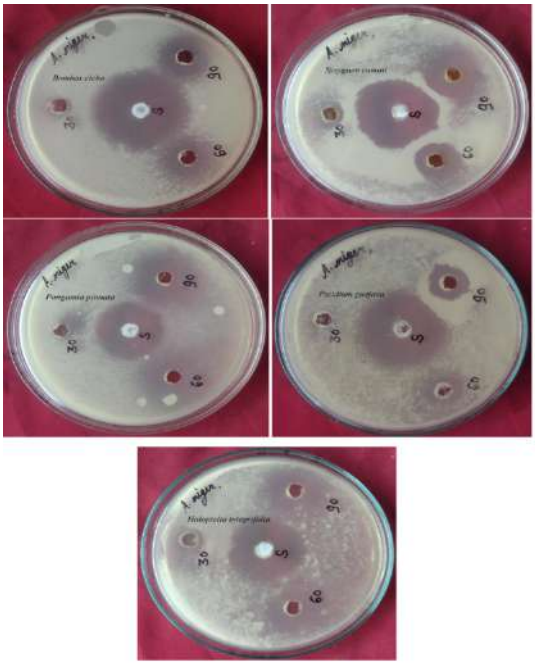

Figure 3: Antifungal activity of methanolic extracts of stem bark of the selected plants against *A. niger.*

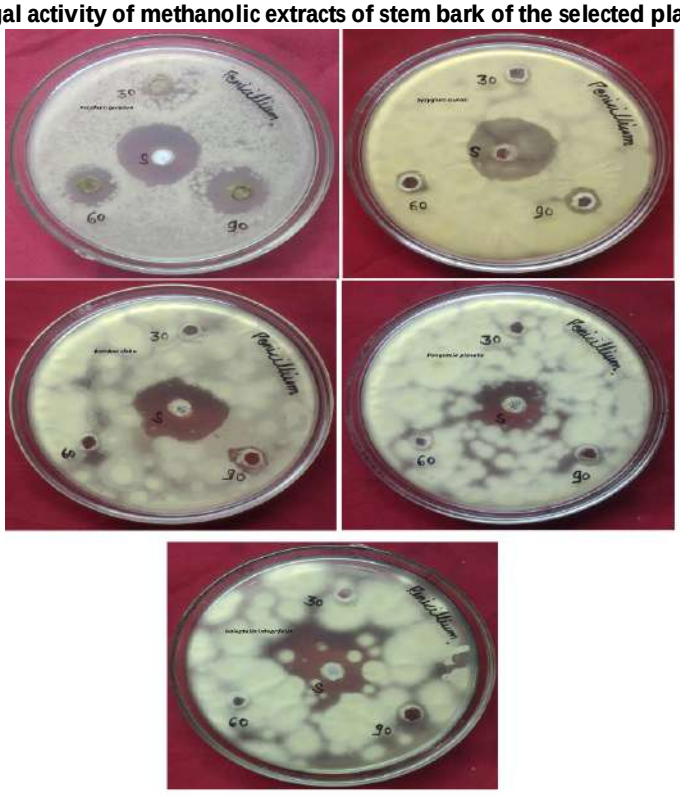

Figure 4: Antifungal activity of methanolic extracts of stem bark of the selected plants against *P. chrysogenum.*

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REVIEW ARTICLE

A Review- Micropellets an Approach towards Novel Drug Delivery System

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ABSTRACT

Pellets are spherical or nearly spherical, free flowing granules with a narrow size distribution, typically varying between 500 and 1500 µm for pharmaceutical applications. They can be divided into desired dose strengths without formulation or process changes, and also be blended to deliver incompatible bioactive agents simultaneously or particles with different release profiles at the same site or at different sites within gastrointestinal tract. The micropellets show a number of additional favorable properties, the most important of which is the larger specific surface area, which results in faster dissolution rates, flexibility in formulation development and when compared with pellets. Micropellets can disperse freely throughout the GIT after administration and consequently the drug absorption is maximized and reduce inter and intra patient variability. Therefore the micropelletization technologies where particles in the size range of 50-1000 µm are generated have been attracting growing attention over the past decade. A new technique is presented here, yields micropellets with a controlled morphology and narrow particle size distribution.

Keywords: Micropellets, Distribution, Pelletization, Cryopelletization, Disintegration

INTRODUCTION [1-3]

Pellets are spherical or nearly spherical, free flowing granules with a narrow size distribution, typically varying between 500 and 1500µm for pharmaceutical applications. They consist of small, free flowing, spherical or semi spherical solid units, typically from about 0.5 mm to 1.5 mm, and are intended usually for oral administration.

It consist of small discrete unit and exhibit some derived characteristics produced by agglomeration of fine powder with binder solution normally the size of the pellets varies from 0.5 – 1.5 mm for oral dosage form. Micropellets that use parentrally acceptable polymers ensure that the entire slow release strategies normally used for solid forms can now be made available for sterile products. Micro pellets are isometric aggregates with smooth surfaces and narrow particle size distribution

METHOD OF MICROPELLETIZATION TECHNIQUES [4-7]

Drug Layering

It includes deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of the identical material or inert starter seeds.

Powder Layering

In powder layering liquid saturation is low and no matter the solubility of the drug within the binding liquid, complete dissolution doesn't occur.

On drying, the binder and other dissolved substance crystallize out and also the liquid bridges are partially replaced by solid bridges. On spraying with binder, fines may develop moisture and enter a nucleate on phase.

Solution and Suspension Layering

In theory, the factors that control coating processes apply on to solution or suspension layering. During solution or suspended within the appliance medium and hence determine the solids contents and thus the viscosity of the liquid sprayed. The strategy continues until the specified layers of drug and hence the target potency of the pellets is achieved. The speed of particle growth is reasonably slow because of the incremental addition of the dissolved or suspended drug. During this process, though the particle population remains the identical, the dimensions of the pellets increase as a function of your time and, as a result, the mass of the system increase.

Extrusion-Spheronization [8-10]

Produces pellets with high loading capacity of active ingredient without producing extensively larger particles and particles of uniform size distribution with good flow properties, Steps involved in Extrusion-spheronization

Dry Mixing

Dry mix of ingredients is completed to grasp solid powder dispersion exploitation Twin shell liquidizer, planetary mixer, and Tumbler mixer.

Wet massing

It's done to produce a spare plastic mass for extrusion, by using traditional instrumentation and method as used in wet granulation for compaction.

Spheronization

It's conjointly named as 'Merumerizer' consists of a static cylinder and a rotating friction plate wherever the extrudate is jerky into smaller cylinders with a length up to their diameter and these plastic cylinders area unit rounded because of resistance forces.

It includes a hatched pattern with grooves running at right angle to a minimum of each different, a radial pattern with grooves running radially from the center of the disc.

Drying

A drying stage is needed therefore on attain the desired wet content. an increase in drying rate provides a lot of porous pellets because of decrease pellet concretion throughout drying method.

Screening
It's a necessity to understand the required size distribution, and for this purpose sieves area unit used.

Cryopelletization [11,12]
Pellets here area unit usually made by permitting droplets of liquid formulation like resolution, suspension or emulsion to come committed refrigerant at -160°C among that range seven used as curing medium. The procedure permits physical change of the material being processed due to speedy heat transfer that happens between the droplets therefore the chemical element for producing a temperature of resolution or suspension being processed. The pellets area units dried in typical freeze dryers to induce eliminate water or organic solvents

Compression [13]
It's one variety of compaction technique for making ready pellets. Pellets of definite sizes and shapes area unit ready by compacting mixtures or blends of active ingredients and excipients enclosed. The formulation and method variables dominant the quality of pellets ready area unit quite like those utilized in tablets producing.

Balling [14]
It is pelletization method throughout that pellets area unit shaped by a nonstop rolling and thumbing motion in pans, discs, drums or mixtures. the strategy consists of conversion of finely divided particles in to spherical particles upon the addition of applicable amounts of liquid.

Hot-Melt Extrusion Technology (HME) [15]
It is process of pumping raw materials with a rotating screw under elevated temperature through a die into a product of uniform shape. Rotating screw impose mixing and agitation result in the de-aggregation of suspended particles in the molten polymer resulting in the more uniform dispersion.

Freeze Pelletization [16,17]
Throughout this method, a liquefied-solid carrier/matrix is introduced as droplets into associate inert column of liquid among that the molten solid is incompatible. The liquified solid droplets will move upward or downward among the liquid column relying on the droplet's density with relevancy the liquid among the column. If the density of the molten-solid carrier/matrix may be a smaller quantity than that of the liquid among the column, then droplets area unit introduced from prime of the column and pellets solidify among the bottom portion of the column.

Spray-Drying And Spray-Congealing [18-20]
Spray-Drying
During spray drying, a drug resolution or suspension is sprayed, with or while not excipients, into a hot-air stream generating dry and extremely spherical particles. This improved the dissolution rates and therefore improves the bioavailability of poorly soluble medicine.
The spray dried powder particles ar same, close to spherical and nearly uniform in size. the design and operation of spray drier will influence a final product, like particle size and size distribution, bulk density, porosity, wetness content, flow ability and break ableness

Spray-Congealing (Spray-chilling)
It's the simplest way quite like spray-drying. Spray congealing might even be a method among that a drug is allowed to soften, disperse or dissolve in hot melts of gums, waxes, fatty acids or different melting solids. Beneath acceptable process conditions, spherical solid pellets ar obtained.

Properties of Micropellets [21]
Micropellets show a number of additional favorable properties. The most important of which is the larger specific surface area, which results in faster dissolution rates. The methods of extrusion have a number of advantages:

i. The processes are robust;
ii. They have good reproducibility
iii. They enable the production of pellets with often high loading, high density and narrow size distribution.

1. For Uncoated pellets
a. Uniform spherical size
b. Narrow particle size distribution
c. Good flow property
d. Even surface
e. Low dust formation
f. Ease of coating

2. For Coated pellets
a. Maintain all above properties.
b. Desirable drug release characteristics

Role of Disintergrating Agent in Micro Pellets [22-24]

Disintegrants are agents added to tablet and a few encapsulated formulations to plug the breakup of the tablet and capsule "slugs' into smaller fragments in an aqueous environment there by increasing the available expanse and promoting a more rapid release of the drug substance.Tablet disintegration has received considerable attention as a necessary step in obtaining fast drug release. the strain on the supply of drug highlights the importance of the relatively rapid disintegration of a tablet as a criterion for ensuring uninhibited drug dissolution behavior. Since a compaction process doesn't involve its exposure to wetting and drying, the disintegrant used intra-granularly tends to retain good disintegration activity. There are three methods of incorporating disintegrating agents into thetablet:

1. Internal Addition (Intragranular)
2. External Addition (Extragranular)
3. Partly Internal and External.

In a direct compression process, drug is mixed with a range of excipients, subsequently lubricated and directly compressed into a tablet. commonest tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly within the GI tract (GIT). In more recent years, increasing attention has been paid to formulating not only fast dissolving and disintegrating tablets that are swallowed but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly within the mouth.

Characterization of Micropellets

Drug Entrapment Efficiency [25]

10 mg of Micropellets (# 22 sizes) were accurately weighed and dissolved in 10 ml of 0.1M NaOH and sonicated to suspend. Final volume was finished up to the mark by 0.1M NaOH and an aliquot from the filtrate was analyzed after suitable dilution, using UV/Visible spectrophotometer at 292nm. Drug entrapment efficiency (DEE) was calculated according to the formula: **% DEE= (Actual drug content/ Theoretical drug content) X 100**

Surface Accumulation Study [26]

This study was usually performed to estimate the amount of drug present on the surface of Micropellets which may show immediate release in the dissolution media. 10 mg of Micropellets (# 22 sizes) were suspended in 10 ml of phosphate buffer (pH 6.8), simulating the dissolution media. The samples were stunned briskly for 15 min in a mechanical shaker. The quantity of drug trickle out from the exterior was analyzed spectrophotometrically at 292 nm.

Particle Size Determination [27,28]

The particle size of a pharmaceutical substance is strictly maintained in order to get optimal biological activity. Sieves were arranged in a nest with the coarsest at the top.A sample (10 gm) of the powder was placed on the top sieves. This sieve set is preset to the mechanical shaker device and shaken for a certain period of time (20 minutes). The powder retained on each sieve was weighed. Frequently, the powder was assigned the mesh number of the screen through which it passes or on which it is retained. Average particle size was calculated using the formula:

d avg = $\sum dn / \sum n$

Where, **n=** frequency weight **d=** mean diameter

Scanning Electron Microscopy [29]

Morphology details of the specimens were determined by employing a scanning microscope (SEM). . The samples were scale on specimen studies with double sided tape, and gold-palladium alloy of 120Ao kness was coated on the sample using sputter coating unit in plasma voltage about 20 MA. The sputtering was finished nearly 3 minutes to get uniform coating on the sample to enable good quality SEM images. The SEM was managing at small accelerating voltage of concerning 15 KV with load current of concerning 80 MA

***In-vitro* dissolution studies [30]**

A drug is predicted to release from the solid dosage forms (granules, tablets, capsules etc) and immediately come in molecular solution. This process is termed as dissolution. The dissolution study was administered consistent with the USP (XXIV) paddle method, for Micropellets (in 0.1 N HCl for two h and pH 6.8 phosphate buffer after 2 h) to mimic the cumulative release of drug in stomach, as per the USP general drug release standard for delayed-release dosage form specifications with a paddle speed of 100 rpm at 37 ± 0.5°C in 900 ml of dissolution medium. After 1h the medium was drained without losing the Micropellets and to the beaker 900 ml of pre heated solution of pH 6.8 was added, study was further continued for 9h at 75 rpm. Aliquot of samples were withdrawn at regular interval of your time which was replaced by the identical amount of fresh medium and was assessed spectrophotometrically at a wavelength of 292 nm with a UV spectrophotometer.

Micromeritic Study of Micropellets [31-34]

Crushing Strength

Strength testing was performed in 20 pellets of each formulation with an available radial force apparatus.

Angle of Response

At a specified height funnel was kept vertically in an exceedingly very very stand below which a paper placed on tier. the underside of the funnel was closed and stuffed with 15 gm of sample powder in funnel. Then funnel were opened to release the powder on the paper to form a smooth conical heap. The height of the heap was measured by using scale.

Density and Porosity

Densities were derived as follows: a specific quantity ' M ' of pellets was taken and was placed into a measuring cylinder. Volume ' V ' occupied by the pellets was noted without disturbing the cylinder and bulk density was calculated using the subsequent equation:

Bulk Density (Pb) = M/V

The tapping method was accustomed determine the tapped density within which the cylinder containing known amount (M) of pellets was subjected to a group number of taps (approximately 100) until the bed of pellets had reached the minimum. the last word volume after tapping 'Vo ' was recorded and thus the tap density was calculated by the subsequent equation:

Tapped Density (PP) = M/Vo

Moisture Content

Weighed quantity of the Micropellets were placed in watch glass and dried to constant weight during a awfully popular air oven at 25-300C.The moisture content (MC) was deduced as difference between the initial (WO) and final weight (Wf) of the Micropellets expressed in percentage and calculated by given formula.

Friability

Resistance to abrasion was determined using USP method for measurement of tablet friability. Accurately weighed quantity of Micropellets sample was placed in Rochefriabilator. Drum was rotated 100 times, and Micropellets were removed. After dedusting, weight loss from the sample was measured by sieving the Micropellets through #85 sieves.

$$\textbf{Friability (\%)} = \frac{\textbf{Final weight- Initial weight X 100}}{\textbf{Final weight}}$$

Kinetics Study of Micropellets [35-37]

Different dissolution data were plotted in different kinetic models (zero-order, first-order, Higuchi and korsmeyer) to interpret the release profile from the coated pellets. The dissolution data were well fitted to Korsmeyer equation (Equation 1), which was useful to describe the drug release behavior from polymeric systems.

Log (Mt / Mf) = Log k + n Log t ……..Equation (1)

Where, 'Mt / Mf' is the fraction of drug released at time t, 'k' is the release rate constant; and 'n' is the release exponent indicative of the mechanism of drug release. The n value is used to characterize different release mechanisms of drug from the dosage forms. In a sphere the value of $n \leq 0.43$ indicates Fickian (case I) release; > 0.45 but < 0.85 for non-Fickian (anomalous) release; and > 0.85 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain whereas anomalous transport (non-Fickian) refers to acombination of both diffusion and erosion controlled drug release. Mean dissolution time (MDT) was calculated from dissolution data using the following Equation 2 (Mockel and Lippold).

MDT= (n / n+1).k -1/n ……Equation (2)

Stability Studies [38]

Paracetamol and omeprazole pellets in screw-capped amber glass bottles were stored for six months at three different conditions, mentioned in Table 1. The humidity was controlled by saturated salt solutions 10-13.

The samples taken at different time intervals, before starting experiment, 1, 2, 4, and 6 months, were analyzed to determine active drug contents.

Factors Affecting Pelletization Technique [39-44]

Moisture Content:

Moisture within the wet mass brings cohesiveness to powder therefore the wet mass are extracted and spheronizer to relinquish spherical shape. High moisture contents end in agglomeration of pellets during the tactic of spheronization.

Rheological Characteristics

The optimum rheological condition finally finally lands up in good flow ability so on extrudate the wet mass

Solubility of Excipients And Drug In Granulating Fluid

Soluble drug get dissolve in an exceedingly very granulating liquid. Thus increasing the number of liquid phase finally winds up in over wetting of pellets. But increase in wetting liquid increases plasticity but includes sticky mass.

Composition of Granulating Fluid

Besides water, alcohol, water to alcohol mixture, anesthetic agent agent, dilute acid, isopropanol is used as a granulating liquid. Aqueous polymer dispersion containing HPMC, PVP, etc can even be used as granulating fluid.

Physical Properties Of Starting Material

Quality of pellets depend not only composition but also on different grades of the identical product. The swelling property of cloth utilized in pelletization technique decides the discharge rate of drug in pellets. It affects the dimensions, hardness, sphericity and density of pellets

Speed of Spheronizer:

It affects the size, hardness, sphericity and density of pellets. The high speed gives high sphericity, lower friability, smooth surface and better crushing strength.

Advantages of Micropellets

- ✓ Spheres have excellent flow properties. This becomes very useful in automated processes or in processes where exact dosing is required, e.g. tableting, moulding operations, capsule filling, and packaging [45, 46].
- ✓ Prevention of dust formation leading to an improvement of the strategy safety, as fine powders can cause dust explosions therefore the respiration of fines can cause health problems [47].
- ✓ They'll be blended to deliver incompatible bioactive agents simultaneously and/or to provide different release profiles at the identical or different sites within the gastrointestinal (GI) tract [48].

Disadvantages of Micropellets

- ✓ Pellets filling involve capsule filling which may increase the prices [49].
- ✓ Tableting of pellets destroy film coating on the pellets [50]
- ✓ The scale of the pellets may vary formulation to formulation but usually is in range, of 0.05 mm and a pair of mm [51].
- ✓ it's difficult to compress pellets into tablets as they're too rigid. Therefore, they're often delivered encapsulated in hard gelatin capsule shells [52].
- ✓ Pelletization demands highly sophisticated and specialized equipment, thereby increasing the price of producing [53].
- ✓ The control of producing process is complicated with too many process variables similarly as formulation variables [54].

Applications

- ✓ The wide distribution of spherical particles in the gastrointestinal tract limits localized build-up of the drug, avoiding the irritant effect of some drugs on the gastric mucosa [53].
- ✓ Reduce inter- and intra-patient variability [55].
- ✓ Modified-release multiparticulate delivery systems are less susceptible to dose dumping than single-unit dosage forms [56].
- ✓ This technology delivers almost perfectly spherical particles exhibiting a very narrow particle size distribution and excellent flow properties [57].
- ✓ Usually a three step production process so economic and supply chain complexity is substantially reduced [58].

CONCULSION

There are several reasons for attractiveness of those dosage forms: provides increased bioavailability of drug product reduction within the frequency of administration to prolong duration of effective blood levels reduces the fluctuation of peak trough concentration and side effects and possibly improves the particular distribution of the drug. If one were to develop a perfect drug delivery system, two pre-requisites would be required. Firstly single dose for the duration of treatment whether for days or weeks like infection. Second it should deliver the active entity on to the positioning of action minimizing the side effects

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Table: 1 Storage conditions for stability studies

S.NO	Temperature (°C)	Relative Humidity (RH %)	Salt Solution to Control Relative Humidity
1.	30 ± 2	65 ± 5	NaCl
2.	35 ± 2	65 ± 5	NaCl
3.	40 ± 2	75 ± 5	KCl

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RESEARCH ARTICLE

On γ Generalized Closed Sets in Neutrosophic Topological Spaces

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ABSTRACT

In this paper a new concept of neutrosophic closed sets called neutrosophic γ generalized closed sets is introduced and their properties are thoroughly studied and analyzed. We have discussed some new interesting theorems and characterizations of γ generalized closed sets in neutrosophic topological spaces. Mathematics Subject Classification (2000): 54A40, 03E72

Keywords: Neutrosophic set, neutrosophic topology and neutrosophic γ generalized closed sets.

INTRODUCTION

Zadeh[13]. introduced and studied truth, the degree of membership and defined the fuzzy set theory. The falsehood, the degree of non-membership was introduced by Atanassov[1]. in an intuitionistic fuzzy set. Coker[3]. developed intuitionistic fuzzy topology. Neutrality, the degree of indeterminacy as an independent concept was introduced by Floretin Smarandache[5]. Neutrosophic topology was introduced by A. A. Salama and S. A. Alblowi[10]. Further the basic sets like neutrosophic open sets(N-OS), neutrosophic semi open sets(N-SOS), neutrosophic pre open sets(N-POS), neutrosophic α open sets(N- αOS), neutrosophic b(γ) open sets(N- b(γ)os), are introduced in neutrosophic topological spaces and their properties are studied by various authors[6,12].. D. Andrijevic [2]. introduced b(γ) open sets in topological space. S.Prema and D.Jayanthi[9]. introduced γ generalized closed sets in intuitionistic fuzzy topological spaces. The main aim of this paper is to introduce and investigate a new concept of neutrosophic closed sets called neutrosophic γ generalized closed sets.

Preliminaries

In this paper (X, τ) is the neutrosophic topological space .Also the neutrosophic interior is denoted by N-int(A), neutrosophic closure is denoted by N-cl(A) and the complement of a neutrosophic set A is denoted by N-C(A) and the empty and whole sets are denoted by 0_N and 1_N respectively.

Definition 2.1: Let X be a non-empty fixed set. A neutrosophic set (NS) A is an object having the form $A = \{\langle x, \mu_{A(x)}, \sigma_{A(x)}, \nu_{A(x)}\rangle : x \in X\}$ where $\mu_A(x)$ represent the degree of membership , $\sigma_A(x)$ represent the degree of indeterminacy and $\nu_A(x)$ represent the degree of non-membership respectively of each element $x \in X$ to the set A.
A Neutrosophic set $A = \{\langle x, \mu_{A(x)}, \sigma_{A(x)}, \nu_{A(x)}\rangle : x \in X\}$ can be identified as an ordered triple $\langle \mu_A, \sigma_A, \nu_A \rangle$ in]-0, 1+[on X.

Definition 2.2: Let $A = \langle \mu_A, \sigma_A, \nu_A \rangle$ be a NS on X, then the complement N-C(A) may be defined as
1. $N\text{-}C(A) = \{\langle x, (1-\mu_A(x)), (1-\nu_A(x))\rangle : x \in X\}$
2. $N\text{-}C(A) = \{\langle x, \nu_A(x), \sigma_A(x), \mu_A(x)\rangle : x \in X\}$
3. $N\text{-}C(A) = \{\langle x, \nu_A(x), (1-\sigma_A(x)), \mu_A(x)\rangle : x \in X\}$

Note that for any two neutrosophic sets A and B,
4. $N\text{-}C(A \cup B) = N\text{-}C(A) \cap N\text{-}C(B)$
5. $N\text{-}C(A \cap B) = N\text{-}C(A) \cup N\text{-}C(B)$

Definition 2.3: For any two neutrosophic sets $A = \{\langle x, \mu_A(x), \sigma_A(x), \nu_A(x)\rangle : x \in X\}$ and $B = \{\langle x, \mu_B(x), \sigma_B(x), \nu_B(x)\rangle : x \in X\}$ is
1. $(A \subseteq B) \Leftrightarrow \mu_A(x) \le \mu_B(x), \sigma_A(x) \le \sigma_B(x)$ and $\nu_A(x) \ge \nu_B(x)$ $\forall$ $x \in X$
2. $(A \subseteq B) \Leftrightarrow \mu_A(x) \le \mu_B(x), \sigma_A(x) \ge \sigma_B(x)$ and $\nu_A(x) \ge \nu_B(x)$ $\forall$ $x \in X$
3. $(A \cap B) = \langle x, \mu_A(x) \wedge \mu_B(x), \sigma_A(x) \wedge \sigma_B(x)$ and $\nu_A(x) \vee \nu_B(x)\rangle$
4. $(A \cap B) = \langle x, \mu_A(x) \wedge \mu_B(x), \sigma_A(x) \vee \sigma_B(x)$ and $\nu_A(x) \vee \nu_B(x)\rangle$
5. $(A \cup B) = \langle x, \mu_A(x) \vee \mu_B(x), \sigma_A(x) \vee \sigma_B(x)$ and $\nu_A(x) \wedge \nu_B(x)\rangle$
6. $(A \cup B) = \langle x, \mu_A(x) \vee \mu_B(x), \sigma_A(x) \wedge \sigma_B(x)$ and $\nu_A(x) \wedge \nu_B(x)\rangle$

Definition 2.4: A neutrosophic topology (NT) on a non-empty set X is a family τ of neutrosophic subsets in X satisfies the following axioms:
(NT_1) $0_N, 1_N \in \tau$
(NT_2) $G_1 \cap G_2 \in \tau$ for any $G_1, G_2 \in \tau$
(NT_3) $\bigcup G_i \in \tau$ $\forall \{G_i : i \in J\} \subseteq \tau$

In this case the pair (X, τ) is a neutrosophic topological space (NTS) and any neutrosophic set in τ is known as a neutrosophic open set (N-OS) in X. A neutrosophic set A is a neutrosophic closed set (N-CS) if and only if its complement N-C(A) is a neutrosophic open set in X.
Here the empty set (0_N) and the whole set (1_N) may be defined as follows:
$(0_1) = \{\langle x,0,0,1\rangle : x \in X\}$
$(0_2) = \{\langle x,0,1,1\rangle : x \in X\}$
$(0_3) = \{\langle x,0,1,0\rangle : x \in X\}$
$(0_4) = \{\langle x,0,0,0\rangle : x \in X\}$
$(1_1) = \{\langle x,1,0,0\rangle : x \in X\}$
$(1_2) = \{\langle x,1,0,1\rangle : x \in X\}$
$(1_3) = \{\langle x,1,1,0\rangle : x \in X\}$
$(1_4) = \{\langle x,1,1,1\rangle : x \in X\}$

Definition 2.5: Let (X, τ) be a NTS and $A = \{\langle x, \mu_A(x), \sigma_A(x), \nu_A(x)\rangle : x \in X\}$ be a NS in X. Then the neutrosophic interior and the neutrosophic closure of A are defined by
$N\text{-}int(A) = \cup\{ G / G \text{ is an N-OS in X and } G \subseteq A \}$,

N-cl(A) = ∩{K/ K is an N-CS in X and A ⊆ K}.

Definition 2.6: A neutrosophic set A of a NTS X is said to be
(i) A neutrosophic pre-open set (N-POS) if A ⊆ N-int(N-cl(A))
(ii) A neutrosophic semi-open set (N-SOS) if A ⊆ N-cl(N-int(A))
(iii) A neutrosophic α-open set (N-αOS) if A ⊆ N-int(N-cl(N-int(A)))
(iv) A neutrosophic regular open set (N-ROS) if N-int(N-cl(A)) = A
(v) A neutrosophic b open set (N-bOS) if A ⊆ N-int(N-cl(A))U N-cl(N-int(A)).

Definition 2.7: A neutrosophic set A of a NTS X is said to be
(i) A neutrosophic pre-closed set (N-PCS) if N-cl(N-int(A)) ⊆ A
(ii) A neutrosophic semi-closed set (N-SCS) if N-int(N-cl(A)) ⊆ A
(iii) A neutrosophic α-closed set (N-αCS) if N-cl(N-int(N-cl(A))) ⊆ A
(iv) A neutrosophic regular closed set (N-RCS) if N-cl(N-int(A)) = A
(v) A neutrosophic b closed set (N-bCS) if N-int(N-cl(A))∩ N-cl(N-int(A)) ⊆ A.

Definition 2.8: Consider a NS A in NTS. The Neutrosophic γ interior & Neutrosophic γ closure of A are defined as
N-γint(A)= U{ G/G is a N-γOS in X and G ⊆A}
N-γcl(A)= ∩{ K/K is a N-γCS in X and A ⊆ K}

Definition 2.9: Consider a NS A in NTS. Then it is a Neutrosophic generalized closed set (N-GCS) if N-cl (A) ⊆ U whenever A ⊆ U and U is a NOS.

Definition 2.10: Consider a NS A in NTS. Then it is a Neutrosophic generalized gamma closed set (N-GγCS) if N-γcl (A) ⊆ U whenever A ⊆ U and U is a NOS.

γ generalized closed sets in neutrosophic topological spaces
In this section we have introduced Neutrosophic γ generalized closed sets and studied some of their properties.

Definition 3.1: An Neutrosophic set A in a NTS (X, τ) is said to be a neutrosophic γ generalized closed set (N-γGCS) if N-γcl(A) ⊆ U whenever A ⊆ U and U is a N-OS in (X, τ).
The family of all N-γGCSs of a NTS (X, τ) is denoted by N-γGC(X).

Example 3.2: Let X = {a, b} and G_1 = ⟨x, ⟨x, (0.5_a, 0.6_b), (0.5_a, 0.4_b), (0.5_a, 0.4_b)⟩ and G_2 = ⟨x, (0.4_a, 0.3_b), (0.6_a, 0.7_b), (0.6_a, 0.7_b)⟩.Then τ = {0_N, G_1, G_2, 1_N} is a NT on X. Here
Let = ⟨x, (0.3_a, 0.2_b), (0.7_a, 0.8_b), (0.7_a, 0.8_b)⟩ be any NS in X. Then A is called a N-γGCS in X.

Proposition 3.3: Every N-CS is a N-γGCS in (X, τ) but not conversely in general.
Proof: Let A be a N-CS in X. Let we take A ⊆ U where U is said to be a N-γOS in X. As N-γcl (A) ⊆ N-cl(A) = A ⊆ U by hypothesis, we have N-γcl(A) ⊆ U. Thus A is a N-γGCS in (X, τ).

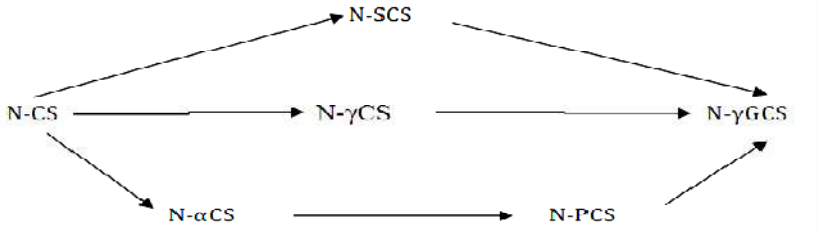
Example 3.4: Let X = {a, b}, G_1 = ⟨x, (0.5_a, 0.6_b), (0.5_a, 0.4_b), (0.5_a, 0.4_b)⟩ and G_2 = ⟨x, (0.4_a, 0.3_b), (0.6_a, 0.7_d), (0.6_a, 0.7_b)⟩. Then τ = {0_N, G_1, G_2, 1_N} is a NT on X. Let A = ⟨x, (0.3_a, 0.2_b), (0.7_a, 0.8_b), (0.7_a, 0.8_b)⟩ is a N-γGCS but not a N-CS in (X, τ) since N-cl(A) = $G_1^c \neq$ A.
Proposition 3.5: Every N-SCS is a N-γGCS in (X, τ) but not conversely in general.
Proof: Let A be a N-SCS in X. Let we take A ⊆ U and U is said to be a N-γOS in X. As N-γcl(A) ⊆ N-scl(A) = A ⊆ U by hypothesis, we have N-γcl(A) ⊆ U. Then A is called a N-γGCS in (X, τ).

Example 3.6: Let X = {a, b}, $G_1 = \langle x, (0.5_a, 0.6_b), (0.5_a, 0.4_b), (0.5_a, 0.4_b)\rangle$ and $G_2 = \langle x, (0.4_a, 0.3_b), (0.6_a, 0.7_b), (0.6_a, 0.7_b)\rangle$. Then $\tau = \{0_N, G_1, G_2, 1_N\}$ is a NT on X.
Let $A = \langle x, (0.3_a, 0.2_b), (0.7_a, 0.8_b), (0.7_a, 0.8_b)\rangle$ is a N-γGCS but not a N-SCS in (X, τ) since N-int(N-cl(A)) = N-int(G_1^c) = $G_2 \not\subseteq A$.
Proposition 3.7: Every N-PCS is a N-γGCS in (X, τ) but not conversely in general.
Proof: Let A be a N-PCS in X & let $A \subseteq U$ where U is said to be a N-γOS in X. As N-γcl(A) $\subseteq$ N-pcl(A) = $A \subseteq U$ by hypothesis, we have N-γcl (A) $\subseteq$ U. Thus A is a N-γGCS in (X, τ).

Example 3.8: Let X = {a, b}, $G_1 = \langle x, (0.5_a, 0.6_b), (0.5_a, 0.4_b), (0.5_a, 0.4_b)\rangle$ and $G_2 = \langle x, (0.4_a, 0.3_b), (0.6_a, 0.7_d), (0.6_a, 0.7_b)\rangle$. Then $\tau = \{0_N, G_1, G_2, 1_N\}$ is a NT on X.
Here we take $A = \langle x, (0.4_a, 0.3_b), (0.6_a, 0.7_b), (0.6_a, 0.7_b)\rangle$ is a N-γGCS but not a N-PCS in (X, τ) since N-cl(N-int(A)) = $G_1^c \not\subseteq A$.
Proposition 3.9: Every N-αCS is a N-γGCS in (X, τ) but not conversely in general.
Proof: Let A be a N-αCS in X. Let as assume $A \subseteq U$ and U is said to be a N-γOS in X. As N-γcl(A) $\subseteq$ N-αcl(A) = $A \subseteq U$ by hypothesis, we have N-γcl(A) $\subseteq$ U. Then A is a N-γGCS in (X, τ).

Example 3.10: Let X = {a, b}, $G_1 = \langle x, (0.5_a, 0.6_b), (0.5_a, 0.4_b), (0.5_a, 0.4_b)\rangle$ and $G_2 = \langle x, (0.4_a, 0.3_b), (0.6_a, 0.7_b), (0.6_a, 0.7_b)\rangle$. Then $\tau = \{0_N, G_1, G_2, 1_N\}$ is a NT on X. Here we take $A = \langle x, (0.3_a, 0.2_b), (0.7_a, 0.8_b), (0.7_a, 0.8_b)\rangle$ is a N-γGCS but not a N-αCS in (X, τ), since N-cl(N-int(N-cl(A))) = N-cl(N-int(G_1^c)) = N-cl(G_1) = $G_1^c \not\subseteq A$.
Proposition 3.11: Every N-γCS is a N-γGCS in (X, τ) but not conversely in general.
Proof: Let A be a N-γCS in X & let $A \subseteq U$ and U is said to be a N-γOS in X. As N-γcl (A)= $A \subseteq U$ by hypothesis, we have N-γcl (A) $\subseteq$ U. Then A is a N-γGCS in (X, τ).

Example 3.12: Let X = {a, b}, $G_1 = \langle x, (0.5_a, 0.7_b), (0.5_a, 0.3_b), (0.5_a, 0.3_b)\rangle$ and $G_2 = \langle x, (0.5_a, 0.6_b), (0.5_a, 0.4_b), (0.5_a, 0.4_b)\rangle$. Then $\tau = \{0_N, G_1, G_2, 1_N\}$ is a NT on X. Let $A = \langle x, (0.6_a, 0.6_b), (0.4_a, 0.4_b), (0.4_a, 0.4_b)\rangle$ is a N-γGCS but not N-γCS in (X, τ) since N-int(N-cl(A))$\cap$ N-cl(N-int(A)) = $1_N \cap 1_N = 1_N \not\subseteq A$.
In the following diagram, we have provided the relation between various types of neutrosophic closedness.



Proposition 3.13: Every N-OS, N-SOS, N-POS, N-αOS and N-γOS are N-γGOS in (X, τ) but not conversely in general.
Proof: Obvious.

Remark 3.14: The union of any two N-γGCSs is need not be a N-γGCS in a NTS X.
Example 3.15: Let X = {a, b}, $G_1 = \langle x, (0.6_a, 0.8_b), (0.4_a, 0.2_b), (0.4_a, 0.2_b)\rangle$ and $G_2 = \langle x, (0.5_a, 0.5_b), (0.4_a, 0.4_b), (0.4_a, 0.4_b)\rangle$. Then $\tau = \{0_N, G_1, G_2, 1_N\}$ is a NT on X.
Let $A = \langle x, (0.5_a, 0.4_b), (0.4_a, 0.5_b), (0.4_a, 0.5_b)\rangle$, $B = \langle x, (0.4_a, 0.6_b), (0.5_a, 0.2_b), (0.5_a, 0.2_b)\rangle$ are N-γGCSs in (X, τ). But $A \cup B$ is not a N-γGCS as $A \cup B = \langle x, (0.5_a, 0.6_b), (0.4_a, 0.2_b), (0.4_a, 0.2_b)\rangle \subseteq G_1$ but N-γcl($A \cup B$) = $1_N \not\subseteq G_1$.
Remark 3.16: The intersection of any two N-γGCSs is not a N-γGCS in general as seen in the following example.

Example 3.17: Let X = {a, b}, $G_1 = \langle x, (0.5_a, 0.7_b), (0.5_a, 0.3_b), (0.5_a, 0.3_b)\rangle$ and $G_2 = \langle x, (0.5_a, 0.6_b), (0.5_a, 0.4_b), (0.5_a, 0.4_b)\rangle$. Then $\tau = \{0_N, G_1, G_2, 1_N\}$ is a NT on X. Let $A = \langle x, (0.5_a, 0.9_b), (0.5_a, 0.1_b), (0.5_a, 0.1_b)\rangle$, $B = \langle x, (0.5_a, 0.7_b), (0.4_a, 0.3_b), (0.4_a, 0.3_b)\rangle$ are N-γGCSs in (X, τ). But A∩B is not a N-γGCS as $A \cap B = \langle x, (0.5_a, 0.7_b), (0.5_a, 0.3_b), (0.5_a, 0.3_b)\rangle \subseteq G_1$ but N-γcl (A∩B) = $1_N \not\subseteq G_1$.

Proposition 3.18: Let (X, τ) be a NTS. Then for every A ∈ N-γGC(X) and for every B ∈ NS(X), A ⊆ B ⊆ N-γcl (A) ⇒B ∈ N-γGC(X).

Proof: Let B ⊆ U and also U be a N-γOS in X. Then since A ⊆ B, A ⊆ U. By hypothesis B ⊆ N-γcl(A). Therefore N-γcl (B) ⊆ N-γcl (N-γcl (A)) = N-γcl (A) ⊆ U, since A is a N-γGCS in X. Hence B ∈ N-γGC(X).

Proposition 3.19: If A is a N-γOS and a N-γGCS in (X, τ), then A is a N-γCS in (X, τ).

Proof: Since A ⊆ A and A is a N-γOS in X, by hypothesis N-γcl (A) ⊆ A. But A ⊆ N-γcl (A). Therefore N-γcl(A) = A. Then A is a N-γCS in (X, τ).

Proposition 3.20: Let (X, τ) be a NTS. Then every NS in (X, τ) is a N-γGCS if and only if N-γO(X) = N-γC(X).

Proof: Necessity: Suppose that every NS in (X, τ) is a N-γGCS in X. Let U ∈ N-γO(X), and by hypothesis, N-γcl(U) ⊆ U ⊆ N-γcl(U). This implies N-γcl(U) = U. Therefore U ∈ N-γC(X). Hence N-γO(X) ⊆ N-γC(X) ⟶(a).

Let A ∈ N-γC(X), then A^c ∈ N-γO(X) ⊆ N-γC(X). That is, A^c ∈ N-γC(X). Therefore A ∈ N-γO(X). Hence N-γC(X) ⊆ N-γO(X) ⟶(b).

From (a) and (b) N-γO(X) = N-γC(X).

Sufficiency: Suppose that N-γO(X) = N-γC(X). Let A ⊆ U and U be a N-γOS. Then U ∈ N-γO(X) and by hypothesis N-γcl(A) ⊆ N-γcl(U) = U, since U ∈ N-γC(X). Therefore A is a N-γGCS in X.

Proposition 3.21: Let (X, τ) be a NTS. Then for every A ∈ N-γGO(X) and for every B ∈ NS(X), N-γint(A) ⊆ B ⊆ A ⇒ B ∈ N-γGO(X).

Proof: Let A be any N-γGOS of X and B be any NS of X. Let N-γint(A) ⊆ B ⊆ A. Then A^c is a N-γGCS and $A^c \subseteq B^c \subseteq$ N-γcl(A^c). Therefore B^c is a N-γGCS which implies B is a N-γGOS in X. Hence B ∈ N-γGO(X).

Proposition 3.22: A NS A of a NTS (X, τ) is a N-γGOS if and only if F ⊆ N-γint(A) whenever F is a N-γCS and F ⊆ A.

Proof: Necessity: Suppose A is a N-γGOS in X. Let F be a N-γCS such that F ⊆ A. Then F^c is a N-γOS and $A^c \subseteq F^c$. By hypothesis A^c is a N-γGCS, we have N-γcl(A^c) ⊆ F^c. Therefore F ⊆ N-γint(A).

Sufficiency: Let F be a N-γCS such that F ⊆ A and F ⊆ N-γint(A). Then $(N\text{-}\gamma int(A))^c \subseteq F^c$ and $A^c \subseteq F^c$. This implies that N-γcl(A^c) ⊆ F^c, where F^c is a N-γOS. Therefore A^c is a N-γGCS. Hence A is a N-γGOS in X.

Proposition 3.23: Let (X, τ) be a NTS. Then for every A ∈ NS(X) and for every B ∈ N-γO(X), B ⊆ A ⊆ N-int(N-cl(N-int(B))) ⇒ A ∈ N-γGO(X).

Proof: Let B be a N-γOS. Then B ⊆ **N-**cl(N-int(N-cl(B))). By hypothesis, A ⊆ N-int(N-cl(N-int(B))) ⊆ N-int(N-cl(N-int(N-cl(N-int(N-cl(B)))))) ⊆ N-int(N-cl(N-cl(N-int(N-cl(B))))) = N-int(N-cl(N-int(N-cl(B)))) ⊆ N-int(N-cl(N-cl(A))) ⊆ N-int(N-cl(A)) as B ⊆ A. Therefore A is a N-POS and by hypothesis, A is a N-γGOS. Hence A ∈ N-γGO(X).

Proposition 3.24: If A is a N-γCS and a N-γGOS in (X, τ) then A is a N-γOS in (X, τ).

Proof: As A ⊇ A, by hypothesis N-γint(A) ⊇ A. But we have A ⊇ N-γint(A). This implies A = N-γint(A). Hence A is a N-γOS in X.

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REVIEW ARTICLE

A Review on Bioremediation with Plants for Removal of Heavy Metals in Industrial Waste water

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ABSTRACT

Heavy metal pollution is one of the major problems of environmental pollution. Toxic metals accumulate into the food chain through food crops and lead to various harmful health issues to human health and the ecosystem. The physical methods are more expensive and less effective. As we know the plants have the inbuilt capability to remediate heavy metals therefore, bioremediation with plants gained much attention in the last few years because of its eco-friendly, inexpensive and effective approach. This review aimed to describe the toxic effects of heavy metals on the ecosystem and human health, the mechanism of plants for accumulating and detoxifying heavy metals as well as various hyperaccumulator plants for accumulating heavy metals from wastewater.

Keywords: Industries Wastewater, Heavy Metals, Inexpensive, Remediation, Hyperaccumulator plant.

INTRODUCTION

Environmental pollution is a global problem that is majorly caused by anthropogenic activities such as using fertilizers and pesticides, deforestation, sewage, industrial effluents. The rate of pollution caused by natural disasters is slower than anthropogenic activity. This result in the release of heavy metals which is very hazardous to natural ecosystem as it accumulates into the food chain and can cause severe health issues to humans and other living creature to their habitats. Over the years, conventional methods like physical, chemical, and thermal processes are used for remediation of polluted sites, but they are mostly ineffective as salts of heavy metal get dissolve in water

hence unable to be separate, Physico-chemical methods are also available but they are very costly (Hussein *et al.,* 2004). However, Bioremediation is a process in which organic wastes are made less toxic and degraded by using natural biological activity. Bioremediation involves the use of microbes, algae, plants, and enzymes to remove heavy metals (Ojuederie *et al.,* 2017). This process has various advantages over conventional methods such as eco-friendly, low-cost, low-technology, and efficient processes. The residues left after treatment are usually harmless products such as carbon dioxide, water, and cell biomass. The well-known hyperaccumulator plants for bioremediation are Brassicaceae and Arabidopsis thaliana, about 25 % of plants belong to these families (Cobbet, 2000). About 300 years ago, the capability of plants for accumulating heavy metals from wastewater is studied (Hartman, 1975). The use of hyperaccumulator plants is majorly conducted in three continents US, Africa, and Asia. In US Environmental Protection Agency's (EPA), Resource Conservation and Recovery Act (RCRA), the Department of Defense (DOD), Department of Energy (DOE) are the national agencies which take care of treating polluted sites. According to the EPA's Comprehensive Environmental Response Compensation Liability Information System (CERCLIS), there are 30,000 polluted sites that are remediated with plants because of its several advantages (Van der Lelie *et al.,* 2001). In 1995 the "Ecological Engineering and Phytoremediation Research Programme" was initiated by AngloGold Ashanti (then Anglo American Gold Division) and the School of Animal, Plant and Environmental Sciences (APES) of the University of the Witwatersrand, Johannesburg (Wits University) are the popular agencies of south Africa which estimated that there are about 140 plant species which are recently used for bioremediation which later can reach up to 200 species after trial.

In India, overexploitation of natural resources is the major issue that gives rise to various problems in which one of which is heavy metal pollution in water bodies as well as in soil. (Kumar *et al.,* 2008) studied phytoremediation process at Pariyej reservoir, an internationally important wetland listed in the Asian Directory of Wetlands, designated as a "Wetland of International Importance" for various plants with respect to heavy metal accumulation also known as biomonitors. He observed Nelumbo nucifera had the highest accumulation of heavy metal whereas the lowest content in the Echinochloa colonum. (Rai, 2008) studied the fern for phytoremediation called Azolla pinnata in which the studies revealed that Azolla pinnata accumulate Hg (II) ions which inhibit its growth and about 70-94% of metal content decreased in the solution. The proper administration for wastewater discharge of industries is very poor which is very harmful to the ecosystem. The textile industries include various steps such as bleaching, dyeing, printing, and finishing steps which include various chemicals and dyes. Majorly azo dyes are used in decolorization procedures in textile industries which are non-biodegradable and highly toxic in nature and contain heavy metals (Kumar *et al.,* 2014). Some of these dyes are Joyfix Red, Remazol Red, Reactive Red, and Reactive Yellow which is persistent and potentially toxic (Kumar *et al.,* 2015). Heavy metals pollution remains in the environment for several years and can cause "direct" or "indirect damage" to lives. Direct damage is caused by a conformation change in biomolecules and indirect damage is caused by producing free radicals of reactive oxygen and nitrogen species. The effects of heavy metals and their permissible limits are listed in (Table 1).

Heavy Metals Harmful Effect on Water Ecosystem

The persistent pollutants are named heavy metals which are majorly produced from a primarily industrial source, a secondary source is an agricultural field by using pesticides, insecticides, fertilizers, and tertiary sources are natural causes such as volcanic activity, soil erosion, geological weathering, etc. Heavy metals bioaccumulate and enter into the food chain to the food web, which can lead to various serious health problems to marine lives, humans, birds, mammals, etc. Metals such as Arsenic, lead, mercury, copper, cadmium, nickel, zinc, chromium, selenium are toxic at very low levels (Cobbina *et al.,* 2015). The toxicity of heavy metals depends upon two factors. The biotic factors include route of exposure, age, gender, nutritional status of individual, tolerance and abiotic factors include organic substances, pH, temperature, alkalinity and hardness, inorganic ligands, interactions (Tchounwou *et al.,* 2012). High concentrations of heavy metals are found in sewage. The sewage treatment process is applied for the removal of heavy metals which is divided into three stages, the first stage include sedimentation and filtration, the second stage requires biofiltration, aeration, or oxidation ponds for the oxidation process, and the last stage deals with the

removal of phosphates and nitrates. Hence, this process is very costly and every industry would not be able to afford so the bioremediation process is advantageous over this process.

Hyperaccumulator Plants for Accumulation of Heavy Metals

The hyperaccumulator plants used in the extraction of heavy metals from water bodies are studied as indicated in (Table 2). The site of heavy metal accumulation differs from one plant to another plant. The maximum accumulation of heavy metal occurs in roots.

Mechanism used by plants for heavy metal accumulation

The common processes used by plants for bioremediation of heavy metals are phytoextraction, phytofiltration, phytostabilization, phytovolatilization, phytodegradation, and Rhizofiltration as listed in (Table 3).The mechanism of uptake of heavy metals basically occurs through roots. There are two types of pathways, the Apoplastic pathway, and the Symplastic pathway. The apoplastic pathway does not require energy whereas the symplastic pathway is the most common pathway which occurs against electrochemical potential gradients and requires energy (peer *et al.,* 2005). In the root cell the channel proteins or H^+-coupled carrier proteins are located in the plasma membrane which is responsible for uptaking and translocating heavy metals.There are basically four families of metal transporter are classified in plants such as ZIP, HMAs, MTPs, and NRAMPs as mentioned in (Table 4).

The plants perform mainly two mechanisms avoidance and tolerance. The avoidance mechanism works at the extracellular level and is called a first-line defense mechanism. Plants either immobilize metal ions, uses a metal exclusion mechanism, release organic acids and amino acids to make ligand for stabilizing metal ions, or change the pH of rhizosphere which causes precipitation of heavy metals to stop reaching metals to other parts of plants (Dalvi and Bhalerao, 2013). However, the tolerance mechanism works intracellular level and it is called a second-line defense mechanism. The heavy metal accumulates in the cytoplasm which detoxifies by making heavy metal ions and ligand chelation which are later on actively transported to the vacuole (Tong *et al.,* 2004) as shown in (figure 1).

CONCLUSION

The industries produce wastewater that is untreated and contains various heavy metals and organic pollutants which emerge concern related health on the environment as well as on terrestrial organisms, aquatic organisms, and humans. The chemical treatment of water is very costly because of which every industry cannot afford. However, bioremediation with plants also called “Green Technology” is a promising approach that is accepted all over the world. However, various limitations are also associated with this method in which one of them is time-consuming. Hence, a single approach is not enough to remediate polluted sites we need a combination of other approaches for valuable results such as the genetic engineering approach, microbes associated approach, enzymes associated approach, etc.

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Table 1: Heavy metal with their impacts along with EPA and Indian standards.

Heavy metals	Impacts	EPA regulatory limit (ppm)	Indian standards mg/l, max
Copper	Liver damage, Wilson disease, insomnia, hepatocellular putrefaction in the liver, headache, and gastrointestinal bleeding.	1.30	3.0
Zinc	Depression, bloody urine, neurological signs and nervous system, continuous vomiting, stomach cramps, abdominal cramps, and pancreatic pain.	0.50	15
Lead	Neurological disorders, skeletal, endocrine, immune systems damage.	15.00	1.0
Cadmium	Kidney damage, liver damage, renal cancer.	5.00	1.0
Nickel	Frank haematuria, renal toxicities, hypothermia, bronchitis, kidney damage, Dermatitis, nausea.	0.20	3.0
Mercury	Damage to kidneys, circulatory system and nervous system, reduced reproductive success, and disrupting endocrine systems.	2.00	0.01
Arsenic	Cardiovascular illnesses, Skin manifestations, visceral cancers.	0.01	0.2
Chromium	Irritation in the stomach and small intestine, respiratory, kidney, liver, headache.	0.10	2.0

Table 2: Heavy metal accumulator Plants.

Name of Plants	Heavy Metal Accumulation	References
Lemna minor L.	Cu, Hg, Zn	(Mo *et al.,* 1989) (Dirilgen *et al.,* 1994)
Hydrocotyle umbellata L.	Cu, Cr, Zn	(Erum *et al.,* 2014)
Myriophyllum spicattum L.	Hg Co ,Cu, Ni, Zn	(Dolar *et al.,* 1997) (lesagea *et al.,* 2007)
Eichhornia crassipes	Cd, Pb, Zn	(Yadav *et al.,* 2015)
Spirodela polyrhiza	Zn, Pb, Ni	(Sharma And Gaur 1995)
Pistia stratitotes	Hg(II) Fe, Cu	(De *et al.,* 1985) (Galal *et al.,* 2018)
Alfaalfa	Ni(II), Cd(II), Cr, Pb,Zn	(Gardea-Torresdey *et al.,* 1996 and 1998)
Water hyacinth	Zn, Cd, Cr	(Delgado And Inel 1993) (Fett *et al.,* 1994)

Azolla filiculoides	Cu, Cd, Pb	(Fogarty *et al.,* 1999)
Hydrilla verticillita	Cr, Cd Ni, Pb	(Phukan *et al.,* 2015) (Zhang *et al.,* 2020)
Potamogeton natus	Zn, Cu, Cd, Pb	(Fritioff And Greger 2006)
Elodea Canadensis	Ni, Cr	(Kahkonen And Manninen 1998)
Azolla pinnata R.Br	Pb, Zn	(Jain *et al.,* 1990)
panicum virgatum L.	Pb	(Dushenkov 1995)
Carex pendula	Pb	(Yadav *et al.,* 2011)
Ipomoea aquatic	Cd, Hg, Pb	(Gothberg *et al.,* 2002)
Salvinia natans	Zn, Cu, Ni, Cr	(Dhir And Srivastava 2011)
Ceratophyllum demersum	Cu, Fe, Ni, Zn	(Borisova *et al.,* 2014)

Table 3: Processes used by plants for remediating Heavy Metals.

Process	**Function**	**Plants**	**References**
Phytoextraction	Plant removes heavy metals by accumulating them from water or soil.	*Brassica nigra* **L.** *Arabidopsis halleri*	(Bharagava *et al.,* 2008) (Claire-Lise and Nathalie 2012)
Phytostabilization	Plants immobilize heavy metals from the enviroment.	*Osmanthus fragrans, Ligustrum vicaryi L., Cinnamomum camphora, Loropetalum chinense var. rubrum, and Euonymus japonicas.*	(Zeng *et al.,* 2018)
Phytovolatilization	Plants uptake heavy metals and release their volatile contaminants in the atmosphere.	*Arundo donax L.*	(Gaurino *et al.,* 2020)
Rhizofiltration	Plants absorb heavy metals from water mainly with the help of roots.	*Pistia stratiotes* L.	(Galal *et al.,* 2018)
Phytodegradation or phytotransformation	Plant uses metabolic processes to degrade the metals which are taken from the environment.	*Phragmites australis* *Azolla filiculoides*	(He *et al.,* 2017) (Zazouli *et al.,* 2014)

Table 4: Types of Heavy Metal Transporters

Metal transporters	**Function**	**Example**	**References**
ZIP	It uptake and transport heavy metals like Fe, Mn, etc from root to shoot	*Thlaspi caerulescens* and *Arabidopsis halleri*	(Assunção *et al.,* 2001)
HMAs	Transport heavy metals like Zn, Cd, Co, Pb and also perform metal homeostasis	*Oryza sativa*	*(lee et al., 2007)*
MTPs	Translocate heavy metals Zn, Ni to	*Arabidopsis halleri and*	(Gustin *et al.,* 2009)

	intracellular and extracellular compartments.	*Noccaea caerulescen*	
NRAMPs	It is resistant associated macrophage proteins that transport heavy metals such as Cu^{2+}, Mn^{2+}, Co^{2+}, Fe^{2+}, and Cd^{2+}	*Thlaspi goesingense*	(Persans *et al.*, 2001)

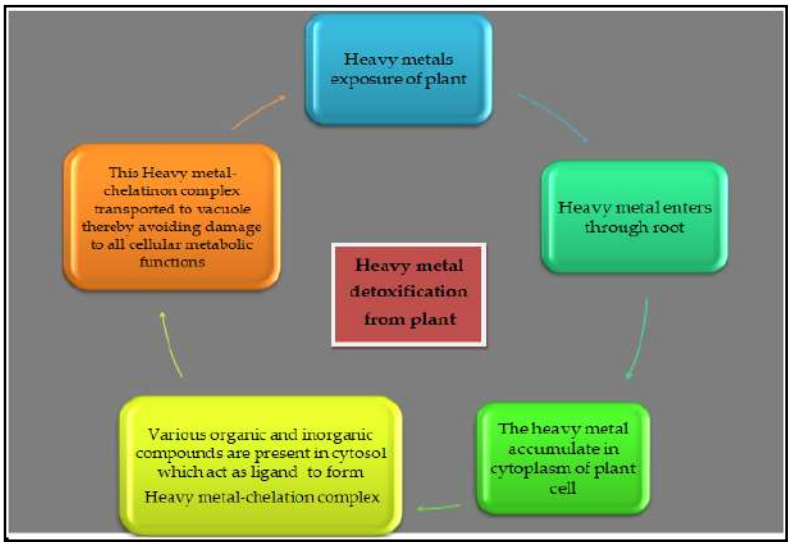

Fig 1: Heavy metal detoxification from plant

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REVIEW ARTICLE

Review on Carbon Nanotubes

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ABSTRACT

Carbon Nanotubes are one the most important materials of future. The plant based hydrocarbon and fossil based hydrocarbon are the main source, for the production of carbon nanotubes. Nanotubes with high quality based on structural and chemical defects will be used for development techniques.The carbon nanotubes are insoluble and contains foreign nanoparticles thus purification process is difficult. This impurities in CNTs will reduce he mechanical and electrical properties. The length of fiber issue, surface area, metal, organics and cell activity are considered to be the toxicological properties of the CNTs. Though the carbon nanotubes has the benefits it also has drawbacks. The CNTs based consumer products plays a vital role in market size and trading.

Keywords: CNTs, nanotubes, properties, impurities, fibers, purification, nanoparticles.

INTRODUCTION[1-3]

Carbon nanotubes are theBucky tubes, in carbon nanotubes carbon molecules are in cylindrical shape and takeexceptional properties that style carbon nanotubes jumble-sale in diverse areas. They have properties like thermal, electrical and mechanical properties. CNTs Discovered in 1991, they have reached a stage of appealing the benefits of several companies worldwide for their large scale production. Carbon nanotubes have fullerene like structure and devising graphene sheets which contain sp2 hybridization of each carbon atom. They possess remarkable electrical, mechanical, optical, thermal and chemical properties, which make them a perfect "fit" for many engineering applications. Several methods of production of carbon nanotubes are discussed outlining their capabilities, efficiencies and possible exploitation as economic large scale production methods. Chemical vapor disposition (CVD) is planned as a probable method for economic large scale production of carbon nanotubes owing

to its relative simplicity of operation, process control, energy efficiency, raw materials used, capability to scale up as large unit operation, high yield and purity.

Carbon Sources[4-8]

One of the key barrier to the industrial application of CNTs, deceptions on the cost of their carbonaceous precursors. Many carbon sources have been used to produce CNTs since its first discovery by Iijima in 1991. Dissimilar methods in making the CNTs show different usage of carbon source. The arc discharge was the first technique cast-off for the production of carbon nanotubes.

The CNTs shaped by this method were full-grown on the negative end of graphite electrode under inert atmosphere of helium or argon with a very high temperature needed in order to fade the pure graphite or evaporate the graphite and metal.There are two main carbon sources for the synthesis of CNTs-using CVD method they are,

a. Fossil-based hydrocarbon
b. Plant based hydrocarbon.

Hydrocarbon was extensive and broadly used as the conventional carbon source in the field of CNTs research. Natural gas becomes the supreme desirable carbon source to numerous researchers. As its stability at high temperature against self-decomposition, methane catalytic decomposition by transition metal catalyst particles is the dominant process in carbon nanotubes growth. Also methane some other carbon species such as acetylene, benzene, xylene, toluene, and so forth, take remained charity as a carbon feedstock to synthesize CNTs.

Classification of CNTs[9-14]

Based on structure, the carbon nanotubes are classified into five types they are,

Single Walled Nano Tube

Most single-walled nanotubes (SWNT) take a diameter of close by to1 nanometre, through a tube length that can be various thousand times the diameter.

Multi Walled Nano Tube

Multi-walled nanotubes (MWNT) involve of multiple layers of graphite moved on themselves to practice a tube shape.

Polymerized SWNT

They are the solid-state exhibition of fullerenes and related compounds and Materials. Several single walled nanotubes intertwine to custom polymerized SWNTs, which are equal to Diamond in terms of inflexibility.

Nanotorus

A nanotorus is a hypothetically defined carbon nanotube set into a torus (donut shape). Nano tori have countless single properties, such as magnetic moments 1000 times larger than earlier expected for firm precise radii.

Synthesis of CNTs[15-19]

High-quality nanotube materials are anticipated for both central and technical applications. High quality denotes to the absenteeism of structural and chemical flaws over an important length scale (e.g., 1–10 microns) lengthways the tube axes. The quantity of patents and publication on the synthesis of carbon nanotube is increasing rapidly. Though there are many encounters remaining that must be resolute concerning synthesis of CNT. Currently, there are four main contests in the field of nanotube synthesis.

a. Mass production, that is, the advance of low-cost, large-scale processes for the synthesis of high-quality nanotubes, together with SWCNTs.
b. Discriminating manufacture, that is, switch over the structure and electronic properties of the fashioned nanotubes.
c. Association, that is, control over the site and alignment of the produced nanotubes on a flat substrate.
d. Instrument, that is, the growth of a detailed empathetic of the processes of nanotube growth. The growth mechanism is motionless a subject of argument, and more than one mechanism might be operative during the creation of CNTs.

A diversity of systems have stayed industrialized to yield CNTs and MWNTs with diverse structure and morphology in laboratory quantities. There are many methods frequently used to synthesize CNTs, they are,

a. Arc expulsion method
b. Laser ablation method
c. Living vapour deposition
d. Fire synthesis method
e. Saline clarification method
f. Sprig pyrolysis method

Some of Characterization Techniques for CNTS

a. Raman spectroscopy
b. Transmission electron microscopy
c. Atomic force microscopy

Purification and Dispersion of Carbon Nanotubes[20-23]

As-synthesized CNTs ready by the overhead means in exorablyen compass carbonaceous impurities and metal catalyst particles, and the volume of the impurities commonly surges with the decrease of CNT diameter. The superfluous difficulties that still exist are,

1. How toeliminate impurities, such as amorphous carbons and metallic catalysts and
2. How togain uniform dispersions of the carbon nanotubes in dispersing media or polymer solutions.

The impurities in unpurified carbon nanotubes strictly diminish the mechanical or electrical properties. The as-produced CNTs soot encompasses a lot of impurities. Up to now, all currently known production methods generate CNTs with impurities. Purification has been an important mock effort subsequently the finding of carbon nanotubes. In overall, the main impurities in the soot are graphite (wrapped up) sheets, amorphous carbon, metal catalyst, and the minor fullerenes. ikewise, structural defects, such as dangling bonds, are repeated lyinitiate in most types of CNTs. These impurities will restrict with most of the desired properties of the CNTs. Purification hitches are significant because CNTs are unsolvable and, hence, liquid chromatography is imperfect. Thus, extensive research has been enthusiastic to the purification of carbon nanotubes in order to confiscate overseas nanoparticles that transform the physicochemical properties of carbon nanotubes

CNTs and its Shape[24, 25]

Countless morphologies of CNTS have been synthesized and pragmatic, which embraces waved, straight, coiled, branched, beaded, and regularly bend structures. Substrates of porous silicon are also secondhand to produce MWCNTs that are grown-up perpendicular to the substrate philanthropic them a straight structure**.** Millimeter high SWCNT arrays were first excellently fabricated by water assisted CVD but the most actual method is direct growing by using a catalytic CVD method, with the involvement of external forces.

CNTs are also found in branched structures approaching letters L, Y, T and more connections which were firstly detected in nanotubes manufactured by arc discharge. CNTs with beads have gotten in changed processes. Beads look as if in dissimilar and they may have both polycrystalline and amorphous graphite.

Toxicological Consideration of CNTs[26]

Centered on the above explanation of CNT synthesis size and composition, attached with the acknowledged toxicology of NP and fibers, we can discourse the toxicological models that could be applicable to CNT.

a. Measurement of the fiber issue
b. Apparent area of the NP issue
c. Metals
d. Organics
e. Go-ahead and cell activation

CNTs and Human Toxicological Effects[27-29]

Outcomes from the toxicological lessons muscularly show that acquaintance to convinced CNTs may be accompanying with longstanding adverse health properties in test-animals. The foremost routes of exposures are by dermal contact, oral uptake and inhalation. Complete effects partly rest on in the ability of the CNT to translocate to supplementary organs in the body

Dermal Effects

Dermal swelling was practical after experience to unpurified SWCNT, but not after introduction to purified SWCNT and commercially available MWCNT. This capacity be triggered by the high echelons of impurities in the unpurified SWCNT pretty than the CNT

Cardiovascular Effects

Nearby amark that pulmonary acquaintance to SWCNT in amalgamation with a high-fat diet indications to plaque progression, and there is suggestion that CNT present in the blood in high concentrations resolveendorse platelet aggregation.

Reprotoxicity

In reprotoxicological tests, CNTs were start not to amass in testis cells later IP injection of CNTs, and injection of CNTs had no properties on male fertility. The worth of the found results is highly dubious, since there is diminutive evidence that CNT will enter circulation at all. However, the results show that even if CNT would enter the body, there are no indications of direct effects of CNT on male fertility. However, reprotoxicological effects have be situatedinitiate for other NMs and official to be most likely caused by indirect effects later pulmonary CNT exposure.

Advantages[30-32]

1. Carbon nanotubes are reception a great deal of courtesy as different matrices for enzyme immobilization.
2. CNTs are restored backing material for enzyme immobilization related to common funding like zirconia, silica, and epoxy.
3. They are more unwavering under harsh condition, provide higher charging of enzyme, and improved catalytic activity of enzyme up to 2-fold larger than level support and up to 10 times advanced than native enzyme.
4. Tremendously small and lightweight, manufacture them excellent substitutions for metallic wires.
5. They are hardy to temperature changes, meaning they function practically just as well in extreme cold as they do in extreme heat

Disadvantages[33-36]

1. In spite of all the research, geniuses unmoving don't recognize exactly how they work. At present, the process is relatively expensive to produce the nanotubes. Extremely small, so are difficult to work with.
2. At the percentage our technology has been charming absolute, it may be a stake to bet on this technology.
3. Would be posh to device this new technology in and change the grownup technology in all the dwelling that we could.
4. The carbon nanotubes themselves are a latent threat to the environment if they are not cautiously monitored.
5. The major concern is their similarity to asbestos fibers, as well as their overall untested status.

Application

Conductive Inks and Layers[37]

Ensuing the line of CNT-containing coatings much exploration has been put into the development of conductive inks, which due to the proportions of the CNT can be made translucent. This possessions is useful for electronic displays and touch screens, and products have most expected go in the market.

Paints and Antifouling Coatings[38]

CNT-based epoxy-paints and antifouling coatings for the marine sector eat been familiarised more than five years back. The claim is that the CNT grounded coating has high strength and enables antifouling properties without discharging toxic substances into the sea water. The decrease of growing organisms on the ships decodes directly into saved fuel and reduced CO2 emissions. CNT-based high-durability epoxy paints are also not compulsory for other resolutions and currently being developed for large windmill blades.

Batteries and Conductive Fillers [39]

The primogenital use may be in Li-ion batteries holding 1 - 3 weight percent CNT in the graphite electrodes. Alternative, speciously well-established use is the application of CNT as a directing filler in base resins and thermoplastics where it can cut the electrostatic charging of plastic parts and qualifying electrostatic painting without further treatment of the materials.

Textiles[40]

CNT additional to textile fibres have been confirmed to hint at electronically conducting properties to the finished textiles, and products applying this property is known on the market in Japan. If they are not already existing in Europe they are likely to developed so in the near future. This may be either as isolated products or as part of these. Electronically conducting textiles are used as really thin heating mats and has been projected used for 'intelligent' clothing e.g. for winter sports applications.

Trade, Market Size and CNT-Based Consumer Products [41-43]

Imitating the wide variety of CNT and their many thought-provoking physicochemical properties, they have a wide range of existing and new potential technological applications asthriving as commercial interest. The symptomatically applied CNT properties are their high tensile strength, electrical conductivity, electrical charge capacity, gas and energy-storage as well as designed motionlessness to high chemical reactivity with applications in the peripheral sensor technology and catalysis. Establishment sources guesstimate a global production of 520 to 3000 metric tons CNT in 2014 with 1750 to 2500 as the intermediary estimate. The construction capacity is many times larger and is estimated to be on the order of 20,000 tons in 2014. The comprehensive group of MWCNT give the impression by far to be the most abundant merchandise shadowed by SWCNT (ca. 5%).

At ECHA, Graph strength C100 (ARKEMA) is registered in the 1-10 tons/year category, where MWCNT from Bayer (now discontinued) and Nanocyl are registered with a creation of 10 – 100 tons/year. The foreseeable global production measurements do not match entirely the CNT ultimatum, which was institute to be on the order of 3,300 – 3,700 tonnes already in 2012. The international trade value of CNT was on the order of $158.6 million in 2014 and is expected to have aonce a year growth rate of 33.4% until 2019. The furthermost important applications are at this time in countless types of composites, electronics, and energy. The application volume and product diversity is growing.Marketable applications of CNTs partake been rather slow to progress, however, predominantlyfor of the high production charges of the best quality nanotubes The CNT properties used is currently mainly their unexpected tensile strength, their electrical conductivity and current carrying capacity, gas and energy storage capacity, and a tunable chemical reactivity from presence inert to reactive with applications in feelers and catalysis.

CONCLUSION

In order to produce CNTs in large scale for commercial application, there are various modified synthesis have been developed. These carbon nanotubes has numerous properties such as electrical, thermal and mechanical which are useful in technology development and in industrial production. The CVD method is considered to be most promising method for the production of large quantity of CNTs. The functionalization and chemistry in CNTs will lead to the better control of CNT based materials, devices at molecular level and the application of carbon nanotubes.

The study of how the linking molecules interact with enzymes and affect the enzyme structure and the arrangement of enzymes on CNTs is necessary. The biomolecules such as enzymes, proteins, DNA/RNA can be interacted and immobilized on CNTs. the new mechanisms and phenomena may continue to appear in future. Concern in this field is fast evolving and is likely to fuel new exciting developments in the near future.

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RESEARCH ARTICLE

Co-ordinate PAL Gene Activity in Response to Agents that Induce Systemic Acquired Resistance

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ABSTRACT

The outcome of any plant- pathogen interaction depends on complex cascades of attack, recognition, & defense reactions at the plant-microbe interface. Within a minute of pathogen recognition, a variety of early events occur in the host such as, ion fluxes across the plasma membrane, cascades of phosphorylation & dephosphorylation and release of reactive oxygen species. Immediately, these events are followed by a broad spectrum of metabolic modifications, that includes a] Stimulation of phenyl propanoid & fatty acid pathways b] Production of defense specific chemical messengers such as salicylic acid (SA) & jasmonic acid (JA) and accumulation of antimicrobial compounds & pathogenesis related (PR) proteins like phenylalanine ammonia lyase (PAL). The phenylpropanoid pathway is considered to be one of the most important metabolic pathways because it leads to the synthesis of a large range of natural products in plants including lignin, lignans, flavonoids and anthocyanins. The first step towards the phenylpropanoid biosynthetic pathway is catalyzed by the enzyme phenylalanine ammonia lyase (PAL) which converts L-phenylalanine to trans-cinnamic acid.

Keywords: phenylalanine ammonia lyase (PAL), Defense mechanism, plant pathogen interaction, *Cicer arietinum.*

INTRODUCTION

An incompatible plant-pathogen interaction is often characterized by a rapid hypersensitive response (HR). The biochemistry of this response is little understood, although the response is thought to be of great importance with regard to the restriction of microbial growth in plant. Metabolic changes, in cells reacting hyper sensitively and in

cells surrounding them, comprises an array of defense reactions such as accumulation of phytoalexins or the synthesis of pathogen related proteins (Vogelsang *et al*., 1994). The outcome of any plant- pathogen interaction depends on complex cascades of attack, recognition, & defense reactions at the plant-microbe interface. Within a minute of pathogen recognition, a variety of early events occur in the host such as, ion fluxes across the plasma membrane, cascades of phosphorylation & dephosphorylations and release of reactive oxygen species (Dixon *et al,* 1994). Immediately, these events are followed by a broad spectrum of metabolic modifications, that includes a] Stimulation of phenyl propanoid & fatty acid pathways b] Production of defense specific chemical messengers such as salicylic acid (SA) & jasmonic acid (JA) and accumulation of antimicrobial compounds & pathogenesis related (PR) proteins (Kombrink & Somssich, 1995).

The phenomenon of SAR suggests that there is a signal that originates at the site of infection and moves throughout the plant. Deen and Kuc (1986) have shown that such a signal is produced by an infected leaf and that detachment of this leaf before the development of the hypersensetive response (HR) blocks the induction of SAR. Grafting and stem girdling experiments with cucumber and tobacco suggest that the SAR signal moves in the phloem (Jenns and Kuc,1979; Gudes *et al*., 1980; Tuzun and Kuc,1985). A great deal of attention has been directed at exploring both, the molecular nature of the SAR protective mechanism and the signaling process by which the local presence of pathogen is communicated to systemic tissues. SAR is associated with the expression of a number of genes, including pathogenesis related (PR) genes, some of which are known or suspected to encode proteins with antimicrobial activity.

In the biosynthesis of phytoalexin, a series of reactions catalyzed by different enzymes are involved. The L-phenylalanine is the precursor and trans-cinnamic acid (TCA) is the first product in this synthetic pathway that synthesizes medicarpin and maackiain along with a large number of phenylpropanoids (Barz and Welle, 1992). The phenylpropanoid pathway is considered to be one of the most important metabolic pathways because it leads to the synthesis of a large range of natural products in plants including lignin, lignans, flavonoids and anthocyanins. The first step towards the phenylpropanoid biosynthetic pathway is catalyzed by the enzyme phenylalanine ammonia lyase (PAL) which converts L-phenylalanine to trans-cinnamic acid. Many workers in the field of plant defense enumerated a long list of explanatory evidences on plant-pathogen interactions, PR – proteins and role of R and *avr.* genes in the interaction. In the light of these evidences, it is clear that defense related genes / gene products are involved in plant defense mechanism of various plant species, directly or indirectly. However, there is very scanty work on *Cicer arietinum-Fusarium oxysporum* system and a little is known about defense mechanism involved, in the system. The approach of this investigation may prove helpful to understand the plant-pathogen interactions and defense mechanisms involved in this system.

The development of disease resistant varieties in chickpea is one of the major breeding objectives in India. The conventional methods used routinely for crop improvement has several limitations and require more time and labour along with exhaustive screening and attention. Moreover, it is not much reliable and may give false results. Therefore, it is essential to develop a more rapid and sensitive method for screening the population of disease resistance at an early stage of plant development. Molecular or biochemical markers are an alternative that would directly give the indication of resistant status at any stage of plant development. Therefore, this investigation has been undertaken to understand host-pathogen interaction involved in *Cicer arietinum-Fusarium oxysporum* systems. This investigation was aimed at achieving following objectives-

- To understand the defense response to *Fusarium oxysporum* in susceptible and resistant cultivars of *Cicer arietinum* L.
- Analysis of defense gene expression and its correlation with resistance status.
- Evaluation of tissue specific expression of these genes.

MATERIALS AND METHODS

In the present investigation, germplasm consisting of four cultivars were procured from Agriculture College of Nagpur and Panjabrao Deshmukh Krishi Vidyapeeth, Akola. Of these, two were reported to be resistant (Jaki-9812, Gulak-1) to *Fusarium oxysporum* while other one cultivar (Chafa-1) is susceptible to it and remaining one cultivar (AKG-46) is moderately resistant to it.

PAL Analysis In seedlings

The induced expression of phenylalanine ammonia-lyase (PAL) analyzed at the seedling stage. For this, seeds of uniform size of four chickpea cultivars such as Chafa-1, AKG-46, Gulak-1 and Jaki-9812, were surface sterilized with 0.05% $HgCl_2$ for 10 min. The sterilized seeds were thoroughly (3X) washed with sterile distilled water. All the operations were carried out aseptically in a laminar air flow bench. The surface sterilized seeds of each cultivar were inoculated separately in sterilized culture tubes (35 x 250mm) containing sterilized moist filter paper. The culture tubes were then plugged and incubated at 25°C in dark. The 10-day old, etiolated seedlings were aseptically sprayed with filter sterilized biotic and abiotic elicitors, using sterile glass atomizer. The biotic elicitors used were, *Fusarium oxysporum* cell wall elicitor (50µg/l) and conidial suspension (23.50×10^5 /ml). The reduced glutathione (100µg/L) was used as abiotic elicitor. The elicited seedlings were then frozen in liquid nitrogen, periodically. For PAL assay, the seedlings were frozen every two hours after elicitation up to 14 hours. The frozen material was stored at –20°C until use. The enzyme Phenylalanine ammonia-lyase (PAL) was assayed according to the procedure given by Lamb *et al*. (1980).

Reagents

Tris buffer (Extraction buffer, L-Phenylalanine (Substrate) solution (12.1mM, D-Phenylalanine (Substrate check) solution (12.1mM Procedure

Extraction of enzyme

Phenylalanine ammonia lyase was extracted from frozen tissue by homogenizing 1 gm tissue in 1 ml ice-cold extraction buffer, in pre-chilled mortar and pestle. To avoid the interference in Spectrophotometric readings, due to the presence of phenolics particularly cinnamic acid, 0.5% (w/v) Polyvinylpyrrolidone (PVP) was added at the time of extraction to remove (adsorb) these phenolics. The extract was centrifuged at 10,000 rpm and clear supernatant was used as enzyme source.

Assay

For assaying PAL, two different sets of each sample were prepared. The vials of first set contained 100 µl enzyme extract 2.9 ml of L-Phenylalanine (substrate) and second set contained 100 µl of enzyme extract and 2.9 ml of D-Phenylalanine solution (substrate check). The blank was prepared for each set separately. The blank of first set contained 100 µl L-Phenylalanine and 2.9 ml extraction buffer and second set contained 100 µl D-Phenylalanine and 2.9 ml extract ion buffer. These vials were then incubated in a water bath, at 40°C for 1 hour. Then absorbance was recorded at every 30 minutes interval up to 2 hours at 290 nm. The assay was done in triplicate. The enzyme activity of PAL was calculated using following formula.

$$\text{PAL activity (µkats/Kg protein)} = \frac{27780 \times (\delta \text{ in absorbance of L-Phe} - \delta \text{ in absorbance of D-Phe})}{\text{mg protein}}$$

Protein Estimation by Protein-Dye Binding Method

The amount of protein in each sample was estimated by protein-dye binding method of Bradford (1976).

RESULTS

Induction of Phenylalanine Ammonia-Lyase in Seedlings

The phenylalanine ammonia-lyase (PAL) is a key enzyme in the biosynthesis of phytoalexin and salicylic acid through phenylpropanoid pathway. All the elicitors used in this investigation were observed to induced the PAL gene expression in different seedling parts of chickpea cultivars. The induced expression of PAL genes in seedlings of resistant cultivars was found to be comparatively more than the seedlings of susceptible cultivars.

Elicitor Response

In general, elicitors of abiotic and biotic origin are known to induce the differential expression of PAL genes in resistant as well as susceptible cultivars. However, the level of expression of defense genes varies with the elicitors used and therefore, the induction of PAL genes by different elicitors was analyzed comparatively. As in resistant cultivars maximum PAL activity was induced between 6 to 8 hours after elicitation, the comparison was made on the basis of induced peak activity during this period only. All the biotic and abiotic elicitors used in this investigation induced the PAL activity in cotyledons and different parts of seedlings of resistant, moderately resistant as well as in susceptible cultivars. However, the biotic elicitor i.e., *Fusarium* conidial suspension were more effective in inducing the PAL gene expression in all the cultivars as compared to *Fusarium* cell wall elicitor and abiotic elicitor i.e., reduced glutathione.

Of the three elicitors used, *Fusarium* conidial suspension induced maximum PAL activity, in the seedlings of all the cultivars. However, the induced PAL activity was more in resistant cultivars than in moderately resistant and susceptible ones. The activity induced by *Fusarium* conidial suspension elicitor in different seedling parts at 6 to 8 hours ranged between 47.12 to 56.85 μKats/kg protein, 41.67 to 46.29 μKats/kg protein and 23.48 to 25.26 μKats/kg protein in resistant, moderately resistant susceptible cultivars, respectively. Other biotic elicitor derived from cell wall of *Fusarium* also induced the PAL activity in seedling parts of different cultivars of chickpea. Effectiveness of this *Fusarium* cell wall elicitor less as compared to *Fusarium* conidial suspension and reduced glutathione. PAL activity induced by this elicitor ranged between 32.94 to 50.65 μKats/kg protein in resistant and moderately resistant cultivars (Jaki-9812, Gulak-1 and AKG-46) while in susceptible cultivar (Chafa-1) it was 18.74 to 19.69 μKats/kg protein (Fig. 30,31,32&33). Abiotic elicitor i.e., reduced glutathione, also induced PAL activity, in the seedlings of all the cultivars. The peak activity induced by reduced glutathione in seedling parts of resistant and moderately resistant cultivars ranged between 40.47 to 53.39 μKats/kg protein whereas in susceptible cultivars it was 21.43 to 26.48 μKats/kg protein. All the seedling parts of resistant, moderately resistant and susceptible cultivars were more responsive to live pathogen as elicitor (Fig. 34,35,36&37).

Response of different Seedling parts

Each seedling part of resistant, moderately resistant as well as susceptible cultivars responded differently for the induction of PAL genes. The response of the seedling parts was found to depend on the elicitor and the cultivar. All the three elicitors induced more PAL activity in cotyledons as compared to other seedling parts. However, the time of induction was different i.e. in cotyledon and root the induction of peak activity is earlier than the peak activity of hypocotyl and epicotyls of all the cultivars .

SUMMARY

Defense Responses in Resistant and susceptible cultivars

The defense response of chickpea cultivars was analyzed at seedling level. The response was analyzed at biochemical level in different seedling parts for the induction of plant defense genes (PAL) by using different elicitors. The analytical data indicated that the response was rapid and these genes expressed at higher level in resistant cultivars (Jaki-9812 and Gulak-1), while the response of moderately resistant cultivar (AKG-46) was slow

and defense genes expressed at relatively low level. The response of susceptible cultivar (Chafa-1) was very slow and defense gene expressed at very low level. Accumulation of salicylic acid in all the cultivars of chickpea was also differential in resistant and susceptible cultivars.

Role of Defense Related Gene products

The role of PAL, a key enzyme has been implicated in the biosynthesis of salicylic acid. It is a signaling molecule in systemic acquired resistance. The increased activity of PAL can be correlated with the increased level of salicylic acid, which resulted in rapid induction of PR-proteins.

DISCUSSION

The expression of plant defense genes has been analyzed in different seedling parts *viz*. Hypocotyl, epicotyl, root and cotyledons. In chickpea different elicitors were found to induce the PAL gene expression at various degrees in different seedling parts. The tissue specific expression of PAL genes was found to depend on the cultivar and the elicitor used. In resistant and susceptible cultivars, All the elicitors induced maximum expression in cotyledons and root respectively. The attainment of peak activity was also found to be at different times in various seedling parts after elicitation. From this, it is evident that the expressions of PAL genes after elicitation vary from organ to organ (tissue specific) as well as it also varied with the elicitor to elicitor in the same organ. Similar results were reported by Billett & Smith (1980) in gherkin seedlings with blue light. They reported that more PAL activity was induced in cotyledons followed by roots, while the response of hypocotyl was the least. Tissue and cell specific activity of PAL in transgenic tobacco and potato has also been demonstrated by Beven *et al*. (1989). The tissue specific expression of PAL genes induced in response to single elicitor indicates that the cell surface gears with receptors, specific for recognition of single type of elicitor, are differentially distributed in different seedling parts. As a result, one tissue is able to recognize one class of elicitors molecule more efficiently than the others class of elicitor. This might have probably resulted in differential expression of PAL genes in different organs in response to elicitor treatment.

CONCLUSION

On the basis of observations, made in this investigation, it is concluded that, defense responses induced by biotic and abiotic elicitors are different. Generally, the pathogen derived biotic elicitors induced defense genes more rapidly and at higher level. Here biotic elicitor- *Fusarium* conidial suspension was most effective as compared to other elicitors. Abiotic elicitor – reduced glutathione is more effective than biotic elicitor- *Fusarium* cell wall elicitor. The effectiveness of the elicitors also varies from cultivar to cultivar. The seedling study indicates that each part exhibit different response to different elicitor. In general, cotyledons and root followed by hypocotyl are more responsive than epicotyl to all elicitors. Thus, it is also concluded that these genes show tissue specific expression which also depends on the type of elicitor used.

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Table-1: Peak activity of PAL activity (µKats/kg protein) in different seedling parts of chickpea cultivars elicited with biotic and abiotic elicitors.

Cultivars	Control	Elicitors Used		
		F.Con.sus	**FCW**	**Red.glu.**
Cotyledons				
Gulak-1	6.86	56.85	49.29	53.19
Jaki-9812	5.33	55.45	50.65	52.99
AKG-46	5.70	46.29	42.29	45.76
Chafa-1	4.28	23.48	19.69	21.43
Root				
Gulak-1	4.53	51.76	43.80	49.93
Jaki-9812	5.46	54.39	44.23	49.94
AKG-46	4.94	44.71	38.26	42.33
Chafa-1	3.24	24.68	19.87	20.33
Hypocotyl				
Gulak-1	3.56	52.83	36.32	48.36
Jaki-9812	3.34	49.82	37.74	47.32
AKG-46	3.16	42.35	34.81	39.47
Chafa-1	2.20	25.26	20.26	25.73
Epicotyl				
Gulak-1	3.97	52.19	34.76	47.68
Jaki-9812	3.39	50.12	34.47	48.45
AKG-46	3.52	41.67	32.94	40.47
Chafa-1	2.68	24.93	18.74	26.48

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RESEARCH ARTICLE

Biofuels from Microalgae with Special Reference to *Dunaliella*: A Review

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ABSTRACT

Algae are the major primary producers in food chain, have been promising source of fuel and pharmaceuticals and have provided several products of economic importance such as β-carotenes. The high level of lipid and β-carotene renders algae as an excellent model for conducting research on the possibility and sustainability of algal biofuels and biopigments. This review focuses on Algae as a good source of biofuel due to its capability of high biomass generation and high oil content production with special emphasis on microalgae *Dunaliella salina* which has greater conversion efficiency of algal oil into biofuels. Different algae stores algal lipids which also includes Triacylglycerols gets transformed into biofuel by various approaches as discussed in this article. Various approaches of strain improvement through genetic manipulation for lipid production by identifying promising targets for genetic engineering of microalgae are being researched throughout the world for these third generation biofuels.

Keywords: Biomass, Transesterification, Photobioreactor, Downstream processing, transformation**:**

INTRODUCTION

Life on earth originated almost 3.7 billion years ago, whereas photosynthetic life became existent between 3.2 and 2.4 billion years ago which provided the earth's atmosphere with abundant amount of vital atmospheric gas namely oxygen. Researchers believe that first photosynthetic life was aquatic one in the form of algae which originated 2 to 3 thousand million years ago which the Precambrian time was. This form of life represented "cyanobacteria" an elaborately studied class of algae. Algae are simple, embryo-less, large group of plants that includes thalloid as well as several unicellular forms. They are mostly aquatic and a vascular in nature. They contain chlorophyll and are whole sole producers of 50% of oxygen produced by plants worldwide. Additionally they are the major primary producers in food chain, been promising source of fuel and pharmaceuticals, and have provided several products of economic importance such as β-carotenes [1].

The major interest of this article is considering Algae as a good source of biofuel due to its capability of high biomass generation and high oil content production [2]. Lipid content in *D. salina* is found to be 45-55% of gross weight [3] and β-carotene amount being 16% of total dry weight [4]. This high level of lipid and β-carotene renders algae as an excellent model for conducting research on the possibility and sustainability of algal biofuels and biopigments. Major benefits of using microalgal cultures are as follows:

1. Microalgal cultures show high growth rates as compared to traditionally used terrestrial plants. Also they provide an advantage of minimal use of land resource.
2. Less input in form of water and chemical fertilizers is required.
3. They have higher efficiency of CO_2 consumption and thus benefit in CO_2 mitigation.
4. Microalgae cultivation is highly cost effective in comparison to conventional farming.

One such algae of research interest is *Dunaliella salina*. Michel Felix Dunal first discovered this splendid microalga in 1838 but it was not until 1905 when Teodoresco proposed its name. Genus *Dunaliella* falls under the phylum Chlorophyta, order Volvocales and family Polyblepharidaceae. Other best-known members belonging to same genus are the species of *Dunaliella tertiolecta, Dunaliella primolecta, Dunaliella viridis, Dunaliella bioculat, Dunaliella acidophyla, Dunaliella parva and Dunaliella media. Dunaliella salina* and some of the other species exhibit life cycle complexity which, in addition to division of motile vegetative cells, also shows the possibility of sexual reproduction (isogamy with a conjugation process). Its body form is pear shaped and absence of rigid cell wall is a striking feature of these particular algae which is compensated by the presence of a rather elastic plasma membrane known as "the pellicle". *Dunaliella* cells have other organelles typical to Chlorophyta: membrane-bound nucleus, mitochondria, vacuoles, Golgi apparatus and an eyespot *D. salina* can grow under high-light intensity, high temperatures, and a wide pH range. It has a high accumulation of lipids and carotenoids [5].

It belongs to the group of "microalgae" since it is unicellular green algae and grows copiously under conditions of high salinity (35% w/v). *Dunaliella* has proved to be an ideal candidate for the study algal adaptation to salinity stress. The studies conducted on *Dunaliella* species have laid the foundation stone of the concept of compatible organic solutes. The mechanism by which *Dunaliella* cells can alter its intracellular glycerol concentration provides it with an ability to thrive in wide range of salt concentrations. It's fascinating biotechnological applications can be attributed to its ability to hyper-accumulate β-carotene by some of the strains under ambient growth conditions. Apart from β-carotene it also contains violaxanthin, neoxanthin, zeaxanthin and lutein it imparts brilliant pinkish color to the hyper saline water body where it grows. "*Dunaliella salina* is the best commercial source of natural β-carotene among all organisms in the world"[6]. It has a capability of accumulating high amounts of β-carotene which could be as high as 14 % of total dry weight in the form of droplets within the chloroplast in order to avoid chlorophyll photo-damage, when culture conditions are of high light intensity, high temperature, high salinity and deficiency of nutrient [7].

Importance of biofuel production with relevance to science and society

Biofuel is a term used for fuel in the form of liquid or gas which is obtained from naturally occurring biomass. Biomass can be used in production of fuels like bio-ethanol and biodiesel which would be future replacement of conventional options like petrol and diesel. By the year 2050, developing countries will inhabit 90% of the world population. Biofuel will prove to be a cost effective and sustainable solution of rising fuel demand in future. Compared with terrestrial crops algal biofuels have a greater yield, they have a capability to produce 30–100 times more energy per hectare [8]. Biofuels and petroleum feed stocks vary greatly in oxygen content. Biofuels have oxygen levels ranging from 10% to 45%, while petroleum has 0%, and hence the chemical properties of biofuels and petroleum are different. Biodiesel comprises of long-chain fatty acid alkyl esters derived from vegetable oils, recycled cooking greases, or animal fats. Liquid biofuels put into use for transportation has gathered appreciation in various countries around the globe because of their renewability, sustainability, availability, regional development, establishment of rural manufacturing jobs, lowering greenhouse gas emissions, and their biodegradability [9].

Bioethanol also can be considered as an excellent biofuel. Its energy equivalent is 68% lower than petroleum fuel, but it is cleaner source of fuel (because it contains oxygen) and thus proves to be potential biofuel alternative to petrol. Ethanol is mixed with petrol in the concentration range 10–85% (v/v).Recently; ethanol is recognized as a fuel for the direct ethanol fuel cells (DEFC) and biofuel cells. Economic benefits of biofuel are such as more jobs in rural sector, investments in plant based industries, lesser Green House Gases emissions, lesser dependency on crude oil, and providing sustainable agriculture. Experts suggest that present oil and gas reserves would last only a few decades. To fulfill this increasing energy demand, fuels such as biodiesel and bioethanol would prove to be the savior. Biofuels are the hope for future in resolving the ever rising demand of conventional fossil fuels, to relieve the environmental impact, and to ensure sustainable energy resource. Bioethanol and biodiesel use would save the world from the future ill impacts of rising fossil fuel consumption and promote balance between agriculture, social, economic, political, and environmental developments [10].

It is also known that use of biofuels can aid to achieve energy security by lowering dependency on oil imports and reducing oil price volatility. Biofuels produced from waste (including latest synthetic fuels which are produced by processes such as hydrogenating CO_2 recycled from emitted flue gases from power plants) can be used for energy storage. "This is a plus point over the availability of energy from infrequent renewable energy sources such as wind and solar" [11]. Exploiting the natural sources of biofuels would be a milestone in solving the global energy demand crisis. Several countries have begun to consider biofuels as their fuel for future and their native plants being significant feeds for the same. In 2018, United States (380888 TMT) being on the top followed by Brazil (21375 TMT) and Indonesia (4849 TMT). Companies working on the algal diesel are Terravia Holdings (Formerly called as Solazyme), Algenol, Blue Marble Production, Culture Biosystem Organization, Oil Inc., Proviron industries, Solix Biofuel, Reliance Life Science. Algenol (Florida) has a stock value of $3.1 million and annual production of 8000 gallons biodiesel per acre of algal harvest. Reliance (India) operates to deliver 100 barrels of biodiesel per day. Works in biofuels are established in developing countries like India and a joint venture are commenced by Williamson Magor Bio Fuel Limited (North East India) and Oils of U.K.

Sources of biofuel

"Bioenergy refers to the energy content in solid, liquid and gaseous products derived from biological raw materials" [12]. Present demand for energy requires extensive use of fossil based fuels which not only are fast depleting but are causing environmental hazards like green house gas emissions which increases global temperature. Thus there arises an ardent need to search for alternative and environment friendly energy sources. One such promising source of alternative energy supply is biofuels. The major biofuels are bioethanol, biobutanol, biodiesel, vegetable oils, biomethanol, pyrolysis oils, biogas, synthesis gas, and biohydrogen. Biofuels can be classified into three generations based on their source [13].

First generation biofuels

These include food crops such as sugarcane, corn and vegetable oils. Feedstock for these biofuels can be categorized as starch and sugar crops (for bioethanol), and oil seeds (for biodiesel).They pose economic and political and natural issues since mass production of bio feed stocks require more agricultural land leading to soil degradation and also cultivation of crops like corn, sugarcane, soybean, potato, beet, soybeans, coconut, sunflower, rapeseed, palm oil, switch grass, Jatropha, Camelina, Cassava, etc cause environmental degradation. Thus first generation biofuels are not practical enough.

Second generation biofuels

These include lignocellulosic biomass derived from agricultural and forestry residues and municipal waste. They are obtained from inedible biomass but these biofuels are very expensive to produce since they require hi-end machinery and procedures.

Third generation biofuels

This includes source of biofuel as microalgae. Third generation biofuels are produced from algal biomass and are promising solution for the future fuel demands since they can provide up to 20 times more bio-oil than traditional agricultural yields [14]. Microalgal cells can be used in synthesis of bio-oil, bioethanol, bio-hydrogen and biomethane using thermo chemical and biochemical methods, thus proving to be the most trustworthy biodiesel source [15].

Microalgae as source of biofuel- a solution for future

Microalgae i.e. the third generation of biofuels would certainly be a source of fuel to rely upon in the near future. Lipid, carotenoid, antioxidant, fatty acids, enzyme polymer, peptide, toxin, and sterols are produced by several microalgal species [16]. The lipid content and biomass yield capacity of microalgae is 80% and 7.3 g/l/d based on the dried weight of biomass, respectively [17]. Thus lipid tends to be most crucial precursor of biofuel production. Lipids can be categorized into fatty acids, glycerophospholipids, saccharolipids, sphingolipids, sterol lipids, prenol lipids, glycerolipids and polyketides [18]. They are in the form of different biomolecules such as fats, waxes, sterols, fat-soluble vitamins, monoglycerides, diglycerides, triglycerides and phospholipids. Lipid molecules perform the function of storage of energy and signaling. Triacylglycerols (TAGs) is a type of storage lipid that consists of three fatty acids bound to a glycerol backbone.

The process of its biosynthesis includes three independent steps as - synthesis of fatty acid in the plastid, then assembly of glycerolipid in the endoplasmic reticulum and packaging into the oil bodies. The fatty acid synthesis is catalyzed via multifunctional enzyme complex such as ACCase (acetyl-CoA carboxylase) which catalyses formation of Malonyl-CoA from acetyl-CoA and bicarbonate. Malonyl-CoA group is shifted to Malonyl-ACP (acetyl carrier protein) where an acyl carrier protein malonyltransferase acts as catalyst. Malonyl-ACP plays the role of FAS (fatty acid synthase) which after series of carbon chain lengthening and desaturation reactions generates mainly C16 and C18 fatty acids [19]. These fatty acids comprise the synthetic membranes, organelle membranes and TAG (Triacylglycerols). TAG formation takes place by the sequential acylation of G3P (glycerol-3-phosphate) backbone with three acyl-CoAs, here acyltransferases acts as catalysts. G3P acylation using GPAT (glycerol-3-phosphate acyltransferase) generates LPA (lyso-phosphatidic acid). LPA acylation by the action of LPAT (lysophosphatidic acid acyltransferase) produces PA (phosphatidic acid). PAP (phosphatidic acid phosphatase) catalyzes phosphate group removal from PA to generate DAG (diacylglycerol). The oil synthesis is catalysis takes place by DGAT (diacylglycerol acyltransferase) from DAG to TAG.

TAG storage takes place in the form of fat body (Lipid Bodies) in algal cell. Algal lipid which also includes TAG gets transformed into biofuel. Various types of microalgae contains varying amount of lipids [20].

a) Very high lipid content (lipid content greater than 60% of dry wt.)
   Dunaliella tertiolecta, Porphyridium cruentum, Botryococcus braunii, Nannochloropsis sp., Neochloris oleoabundans and *Chlorella emersonii*
b) Moderate lipid content (40% to 60% of dry wt.)
   Chlorella minutissima, Chlorella protothecoides, Chlorella vulgaris, Chlorella sp., Crypthecodinium cohnii, Dunaliella salina, Isochrysis galbana, Nannochloris sp., Nannochloropsis oculata NCTU-3, Nitzschia sp., Phaeodactylum tricornutum, Scenedesmus dimorphus, Scenedesmus obliquus, Schizochytrium sp. and *Skeletonema costatum*
c) Low lipid content (less than 40%)
   Arthrospira maxima, Ankistrodesmus sp., Chaetoceros muelleri, Chlorella sorokiniana, Cylindrotheca sp., C. cohnii, Dunaliella primolecta, Ellipsoidion sp., Euglena gracilis, Haematococcus pluvialis, Monodus subterraneus UTEX 151, Monallanthus salina, N. oculata, Oocystis pusilla, Pavlova salina, Spirulina platensis, Thalassiosira pseudonana and *Tetraselmis suecica.*

Dunaliella salina contains 6.0–25% Lipid content (%, dry weight) and 116 mg L^{-1} d^{-1} lipid productivity.
Its fatty acid composition constitutes (Carbons) (%)

1. Lauric acid (C12:0) (1.52)
2. Myristic acid (C14:0) (10.125)
3. Palmitic acid (C16:0) (27.26)
4. Stearic acid (C18:0) (1.30)
5. Oleic acid (C18:1) (3.81)
6. Linoleic acid (C18:2) (2.11)
7. Lauric acid butyl ester (gC18:3) (4.79)
8. Arachidic acid (C20:0) (1.66)
9. Behenic acid (C22:0) (0.98)
10. Octadecatetraenoic acid (C18:4) (1.45) [21]

While ***Dunaliella tertiolecta is*** found to ***contain*** 15.20 %(% d wt.) lipid content and 4.3 mg L^{-1} d^{-1} lipid productivity. Its fatty acid composition constitutes (Carbons) (%)

1. Myristic acid (14:0) (1.1)
2. Palmitic acid (16:0) (13.3)
3. Stearic acid (18:0) (0.6) [22]

Production of biofuels from microalgae

Production of biofuels from microalgae is achieved in following steps [22] such as Culturing lipid enriched biomass, Separating biomass from culture medium and medium recycling, Drying or dehydrating biomass, Lipid extraction, Lipid conversion to biofuel, Downstream processing.
Microalgae culture is performed in two types of growth systems-

Open Type /Raceway Ponds

In this kind of system algae is cultured in raceway configuration where a paddlewheel circulates the liquid culture medium along with algal cells. The structure is made up of concrete in a shallow pond (15 to 35 cm deep) style and is cemented or plastic lined to avoid seepage. Water is continuously rotated allowing uniform mixture of nutrients and algal cells which are growing under uniform sunlight and avoid algal cells from settling down. Nutrients are supplied continuously from inlet situated one side and mature algal cells are harvested from the other outlet. The largest raceway-based biomass production. Facility occupies an area of 440,000 m^2 [23]. A generalized diagram of typical raceway pond is shown in Figure 2.

Closed type or Photobioreactor

Photobioreactor provide closed culture environment for growth of microalgal cells. They are a bit expensive but with a benefit of being safe from invasive micro-organism. Lee et al. and Wang et al studied that photo bioreactors have greater efficiency and biomass concentration (2–5 g/L), reduced harvest duration (2–4 weeks), and elevated surface-to-volume ratio (25–125/m) compared to open ponds [24]. These photo bioreactors are used in various arrangements such as tubular, flat-plated, rectangular, continued-stirrer reactor, etc. It is composed of flexible glass or plastic arranged in vertical or horizontal or inclined or helical manner so that it receives maximum illumination surface to volume ratio. Circulation of culture medium is maintained in a turbulent manner in order to provide efficient nutrient distribution, greater gaseous exchange, avoid cell settling and adequate illumination to biomass. A simple depiction of its structure is shown in Figure 3.

Hybrid systems constitute both open ponds as well as closed bioreactor system combined to obtain optimum yield. Open ponds are efficient and easy way for algae cultivation, but they get quickly contaminated by invasive species. This combination is a cost-effective way of culturing microalgae and is helpful in avoiding contamination. Open

ponds are inoculated with desired strain which would be further cultivated in a closed bioreactor however the inoculum concentration should be high enough to supersede contamination by invasive species.

The harvesting method or separating biomass from culture medium is peculiar to species, cell density, and often on the culture conditions. Algae harvesting is done by centrifugation, flocculation or froth flotation. Chemical flocculants such as Alum and $FeCl_3$ are commonly used. Algae grown in brackish or salty water needs some chemical flocculants to induce flocculation. Chemical harvesting method is too expensive for large operations. Also altered CO_2 supply to an algal system can result in algae to flocculate by itself, which is called ‘‘auto-flocculation”. In another method called froth flotation, the algal culture is aerated into froth and algae are then separated from the water. Since huge amounts of water are involved in microalgal culture medium, which is rich in nutrients, thus recycling of nutrients is necessary after cell harvesting. At larger volumes of algae production these left over nutrients prove to be a resource that cannot be neglected, and also disposal of this nutrient rich media would cause disposal problems [24].

Drying is the process to reduce the moisture content from algal biomass. This is done via processes such as sun drying which is the most economical method however more costly methods such as heat sources, spray drying and freeze drying are also being used [25].

Lipid extraction is done after the microalgal cell is disrupted. Microalgae have different types of cell coverings ranging from the ‘naked’ cells of *Dunaliella* which only have a thin outer glycocalyx, to the highly-resistant algenin containing cell walls of *Nannochloropsis* and *Chlorella*, and the silica frustules of diatoms. Methods which have been used for cell lysis include mechanical processes such as bead mills, sonication, cavitation and autoclaving. Among the non-mechanical methods freezing, osmotic shock, enzymatic digestion, use of organic solvents, and acid or base reactions are commonly used. Lipids in majority being hydrophobic molecules (e.g., neutral lipids) interact with relatively non-polar solvents such as ethyl ether, chloroform and benzene, while membrane associated polar lipids require polar solvents like ethanol and methanol to break the hydrogen bonding and electrostatic forces between the lipids and proteins.

The most commonly used lab methods for lipid extraction are-
1. Soxhlet extraction (usually with n-hexane as solvent)
2. Folch [26] and Bligh and Dyer [27] methods which use chloroform and methanol in varying ratios as solvents
3. Using other alcohols such as ethanol, 1-butanol and isopropanol are being developed to replace the methanol [28]
4. Other combinations of co-solvents also have been proposed for the extraction of lipids from microalgae is hexane/ethanol[29]
5. Hexane/isopropanol [30].
6. Combination of ethanol and hexane at a 5:1 v/v ratio in a 2-step extraction procedure.

The economics of the application of these processes on an industrial scale with microalgal biomass is still in question despite of the fact that numbers of methods for lipid extraction are available [31].
The prime focus of algal biofuel is production of liquid fuel such as bioethenol, biodiesel and jet fuel. Microalgal oils or lipids commonly contain free fatty acids, phospholipids, sterols, water, and impurities which prove to be a hindrance in the process of transesterification. The polyunsaturated fatty acids content is also high in this microalga which affects the fuel quality. Thus a chemical alteration such as transesterification, pyrolysis or hydrogenation is required to keep up with the quality standards [32].

The conversion of biomass to biofuel takes place via several procedures depending upon the biofuel component:
Fermentation
Microbial fermentation of algal cells is carried out in order to produce bio-ethanol. *Chlamydomonas reinhardtii* and *Chlorella vulgaris* prove to be excellent carbohydrate source for ethanol production by US Renewable

Fuels Standard(36 billion gallons). *Scenedesmus dimorphus* another alga which produces ethanaol with 53 W/W of carbohydrate with 93% bioethanol yield [33].

Transesterification

Transesterification is a process in which one mole triglyceride reacts with 3 mole of alcohol to produce simple esters and glycerol as by-product. The prime focus of algal biofuel is production of liquid fuel such as bioethenol, biodiesel and jet fuel. Microalgal oils or lipids commonly contain free fatty acids, phospholipids, sterols, water, and impurities which prove to be a hindrance in the process of transesterification. The polyunsaturated fatty acids content is also high in these microalgae which affect the fuel quality. Thus chemical alterations such as transesterification, pyrolysis or hydrogenation are required to keep up with the quality standards [34]. Transesterification process takes place by involvement of both homogenous as well as heterogeneous catalysis however in certain supercritical conditions non-catalytic pathway is also observed.

Homogenous catalysis is performed by the use of conventionally available acids and bases(e.g. H_2SO_4, Noah, KOH, and $KOCH_3$). Alkali catalysts (Noah and KOH) are preferred over acid catalysts due to fast activity, cost effectivity, easy availability and low corrosiveness. The acid catalyst produces a strong electrophile by addition of H+ to carbonyl group whereas the base catalyst produces a strong nucleophile by elimination of proton from the alcohol. Methyl and ethyl esters (biodiesel) are a result of using methanol and ethanol respectively.

Heterogeneous catalysis

Heterogeneous catalysts such as ion exchange resins (e.g.- MOR, HY, HZSM-5, Hβ), sulfated oxides, transition metal or alkaline earth metal or mixed metal oxides(e.g.- ZrO_2, WO_3, CaO, ZnO, $SrCO_3$), carbon-based heterogeneous catalysts, and enzymes have been employed in biodiesel production processes [35]. Transesterification by the use of enzymes is commonly performed by lipases from microbial strains, including *Pseudomonas fluorescen*s, *Pseudomonas cepacia*, *Rhizomucor miehei*, *Rhizopus oryzae*, *Candida rugosa*, *Thermomyces lanuginosus*, and *Candida Antarctica* [36]. Metal oxide nanoparticles containing Immobilized lipases have considerable thermal stability, selectivity and also ease of separation. Biodiesel yield as high as 90% was obtained with enzyme concentration (1%–3.5%).

Hydro Thermal Liquefaction

HTL is a process of conversion of entire algae nutrients including proteins and carbohydrates and not only lipids. Hydrated microalgae can be subjected to liquefaction at very high pressure condition of 25 MPa and at a temperature lower than 375 °C to produce biofuel.

Pyrolysis

Pyrolysis is direct thermal decomposition of biomass at high temperature (400 °C – 1000 °C) in the absence of catalyst and oxygen to produce bio-oil.

Enhancement of biofuel production in microalgae by various strategies-

Presently , 40 000 microalgal species are identified, but this number might exceed 100 000 species, most of whose biochemical composition and metabolism is still unknown [36] . Several factors play crucial role in triacylglycerides (TAG) production of from algae which include, light regime, both photoperiod as well as quality, pH, salinity, and other factors that can be standardized for optimizing the yield obtained from cultured algal biomass [37]. The lipid accumulation of algal genera *Dunaliella, Chlorella, Schizochytrium, Nannochloropsis, Porphyridium, Tetraselmis,* and *Phaeodactylum* are known to dwindle between 20 and 50% [38], and C. vulgaris have shown overwhelming percentage of lipid accumulation of up to 70% [39] but in all cases the lipids production is less .Therefore there arises a need for optimizing productivity and lipids content in algae.

Lipid induction through environmental stimuli

Lipid synthesis is induced by environmental stresses such as light, temperature, and pH, in microalgae. Nutrient deprivation is suitable for steady lipid induction within the culture batch. Lipid induction by nutrient starvation mechanism is still not known but, Nitrogen limitation stimulates acyl hydrolase and phospholipid hydrolysis, which results in decrease in the cellular content of thylakoid membranes and in protein synthesis, which leads to a decrease in cellular growth [39]. Though N_2 limitation is the best effective method to stimulate lipid synthesis but it happens on the cost of growth, which results in reduction of overall productivity. When cultured in controlled N, the green algae *Chlorella sp*., *Parachlorella sp*., *Scenedesmus sp*., *Dunaliella* sp., and *Botryococcus sp*. show change in lipid productivity and accumulation.

Strain improvement through genetic manipulation for lipid production

Strain improvement at genomic level is the new interest for researchers. A change in a genetic trait by (over-) expression or repression of the gene of interest is known as genetic improvement. These changes can be designed through molecular tools, or occur randomly and be selected. Genetic manipulation approaches can classified into three categories according to their technology-

Random mutagenesis

A technique which depends on a chemical or radiation that induces chromosomal lesions, called a mutagen; mutagen treatment results in randomly mutated strains. Since the mutation point cannot be pre-determined, mutagenesis is followed by high-throughput screening for desirable traits, this includes staining with lipophilic fluorescent dyes and fluorescence-activated cell sorting (FACS) for high–lipid-content mutants [40]. Commonly used chemical mutagens include alkylating agents such as ethyl methane sulfonate (EMS) and N-methyl-N′-nitro-nitrosoguanidine (NTG). They were the pioneer chemicals employed in enhancing the production of eicosapentaenoic acid (EPA) in *Nannochloropsis oculata* [41] and to increase the growth properties of *Chlorella* [42] through random mutagenesis. With the new age technology of high-throughput sequencing it is possible to identify the mutation point, and has aided in identifying the major enzymes responsible in lipid production. For example, Ma et al. (2019) sequenced whole genomes of γ-ray irradiated mutant strain in a lipid-abundant mutant of *Scenedesmus* sp. and identified mutations in two key genes involved in lipid biosynthesis pathway [43] and the corresponding wild type. Expressing these two mutated genes in a lipid-poor mutant strain, Ma et al. (2019) increased lipid productivity to a greater extent than that in the lipid-rich mutant strain. This is perfect example of strain improvement through random mutagenesis.

Nuclear transformation for transgenic expression

Nuclear gene transformation is applied to incorporate gene segments into the nucleus for the purpose of either expression or repression (in the case of knockdown by RNA interference). It is primary technique for heterologous gene expression in the host organism. In vitro synthesized gene fragments can be incorporated into the cell by two methods namely physical approach (e.g. glass beads, electroporation, particle bombardment) or using bacterial vector such as *Agrobacterium*. Genetic transformation involves several different processes: DNA penetration into the cell and nucleus, integration into a chromosome, and its transgenic expression. The success of genetic transformation is dependent on efficient expression of a selectable marker gene. Codon optimization, adding and optimizing promoters, intron within the transgene, or changing traits of the host strain are common strategies to avoid problems relating to expression of a transgene.

Genome editing for precise target gene modification

In genome editing, DNA double strand is broken by a nuclease in a sequence-specific manner. For transcription activator-like effector nucleases (TALENs), a specific nuclease is designed for each specific target DNA sequence. Cas endonuclease cuts DNA strand where the guide RNA binds, and the latter can be easily made target specific. For this reason gene editing approach is more inclined towards the use of the CRISPR/Cas system. Gene knock-out using the CRISPR/Cas system is also advantageous over the use of RNAi because it completely annuls the gene product due to

a target-specific mutation in the gene. However this system faces two major drawbacks *viz*. One is the requirement for markers for clone selection and the second being lack of efficient delivery technology. Serif et al. (2018) raised the former problem and developed two endogenous counter-selectable markers, PtUMPS and PtAPT, conferring resistance to 5-FOA (with uracil auxotrophy) and 2-FA (with adenine auxotrophy), respectively, using a selection marker as a knock-in mutation proves to be a feasible alternative [44]. For addressing the latter problem researchers have introduced genes encoding the Cas9 enzyme and guide RNA into microalgal cells in order to produce these molecular tools. Some trials include-

a) Use of episome [45].
b) Improvised versions of Cas enzymes with reduced off-target effects and elevated efficiency have also been reported [46]
c) Bioinformatics tools for finding proper targets and confirming mutations [47].

For the efficient delivery system, the development of micro fluidic technology might bring respite. Efforts are being made for improving exogenous gene delivery successfully into a single cell using nanowire [48] or small cell suspension droplet [49]. Minimal amount of material is required for such systems.

Strategic targets for genetic engineering that have been used to increase lipid content in diatoms.

Promising targets for genetic engineering of microalgae

Enhancing fatty acid and TAG synthesis

Acetyl-CoA carboxylase (ACCase) has been a key enzyme in fatty acid synthesis and thus is a primary target for enhancing lipid content. *Cyclotella cryptica* and *Navicula saprophila* transformants showed a 2- to 3-fold increase in ACCase activity but it did not show an increase in FA content. Among enzymes involved in TAG synthesis, the over expression of diacylglycerol acyltransferase in most cases enhances lipid synthesis [50]. 2 fold Enhancement in lipid production was also achieved through co-expression of five acyltransferases from yeast (*Saccharomyces cerevisiae and Yarrowia lipolytica*) in *Chlorella minutissima* [51]. In case of *Dunaliella salina*, simultaneous over expression of a subunit of ACCase(accD) and malic enzyme (ME), raised total lipid content [52].

Reducing the contribution of competitive pathways

Another effective strategy is inhibiting metabolic pathways which compete against lipogenesis for same resources of metabolism, especially starch biogenesis and lipid catabolism, for example

a) Knockdown of main enzymes involved in the starch synthesis pathway has shown efficiency in increasing lipid accumulation. The starchless mutants of C. reinhardtii (sta-6 and sta7-10 in which ADP-glucose pyrophosphorylase(AGPase) and isoamylase genes are mutated, respectively) have increased total lipid accumulation per cell during nitrogen deprivation [53]
b) In *T. pseudonana*, the suppression of multifunctional lipase/acyltransferase/phospholipase showed a 3.3-fold rise in lipid content compared to the wild type (Trentacoste et al., 2013) [54]. However, disrupting lipid catabolism and starch generation may adversely affect microalgal growth and biomass production [55].
c) In *C. reinhardtii*, a knockout mutant of the phospholipase A2 gene resulted in 64.25% rise in total lipid content [56], whereas another study reported that a 10-fold increase in TAG was achieved when the *cht7* gene (encoding a TAG lipase) was silenced [57].
d) The mutation in *ACX* gene encoding acylCoA oxidase which has a peroxisomal targeting signal, resulted in 20% increase of oil contents in *Chlamydomonas* under nitrogen limited condition [58].

Redirecting metabolic flux through transcription factors

Regulatory signaling pathway may be Manipulated to enhance lipid synthesis, and transcription factors are suitable candidates for the same. The transcription factor bHLH is prime candidate for regulation of cell growth, development, and stress-related behaviors [59]. Over expression of bHLH gene raised biomass and fatty acid methyl ester (FAME) productivity in *Nannochloropsis salina* and, also resulted in rise of rate of growth and nutrient uptake [60]. Over expressing Dof-type TF in *C. reinhardtii* caused two fold increase in total lipid accumulation, indicating that that the *Dof* gene is actively involved in lipid biosynthesis [61]. For the purpose of biodiesel production over expression coupled with nutrient stress enhanced total lipid and the desired specific FA [62].

Also there exist other transcription factors which probably regulate mechanisms of lipid synthesis namely-

a) Accumulation of starch granule and lipid catabolism in response to Pi availability is regulated by PSR1
b) TAG and lipid droplet accumulation is carried out by CHT7 [63],
c) TAR1 resumes growth at the recover from nutrient deprivation [64],
d) RGQ1(a RING-domain protein) regulates responses against N deprivation [65]
e) N deprivation induced TAG accumulation is regulated by NRR1 [66].

A considerable fact is that these TF's have multiple regulatory targets, and unknown interacting partners, therefore need arises for more intensive and comprehensive research to employ these TFs for strain improvement.

Genetic engineering in *Dunaliella salina*

Dunaliella salina has been considered as excellent system for genetic transfers due to following advantages [67] –

1. *D. salina* shows extreme tolerance to varying salt concentrations which ranges from 0.2% to 35%.
2. *D. salina* being a photosynthetic, unicellular organism can be easily cultured on a large scale.
3. It lacks a rigid envelope and thus acts as naked protoplast which facilitates easy gene transfer.
4. It bears a single cup shaped chloroplast which acts as a potentially high-efficiency expression system for large scale production of recombinant proteins.
5. *D. salina* can accumulate significant amounts of carotenoids, lipids, vitamins, and minerals.
6. Recombinant products produced by *D. salina* can be easily recovered by cell lysis.

However expression of transgenes in *D. salina* needs regulatory elements such as promoters, enhancers and terminators. For e.g. Exogenous promoters, cauliflower mosaic virus 35S (CaMV35S) is most frequently used promoter in driving the expression of foreign genes in *D. salina*. Among the endogenous promoters two inducible endogenous promoters have been identified, namely, the upstream region of the nitrate reductase (NR) gene and the duplicated carbonic anhydrase 1 (DCA1) promoter, it aids in screening of transformants of *D. salina*.

Transformation methods of foreign genes in *D. salina* have been shown in TABLE 1.

Nuclear transformation of *D. salina* shows low expression of transgenes and successful products are not obtained however chloroplast expression system are building new research interest e.g. bkt gene incorporation from *Haematococcus pluvialis* encoding β-carotene ketolase (4,4'β-oxygenase) coupled with chloroplast targeting for ketocarotenoids production [68].

National status of *Dunaliella salina* in biofuel production

Commercial scale biofuels and bioproducts are possible due to the availability of some advanced tools for gene manipulation .The microalgae *Dunaliella salina* is found to be a rich source of natural value added products i.e. carotenoids and unsaturated fatty acids. Commercial scale biofuels and bioproducts are possible due to the availability of some advanced tools for gene manipulation . Marine species of *Dunaliella* are deployed in fishing industries, promising a huge and expanding market for fresh, frozen, or dried biomass from algae that accumulate specific compounds of high value-added biomolecules [69].

Biodiesel production from microalgae *Dunaliella salina* is promising source for renewable biodiesel and to meet current fuel demand. Biodiesel yield of around 66.6% was achieved from microalgal biomass of *Dunaliella salina* by direct transesterification process described by Johnson and Wen (2009) also the total lipid content was found to be 27.5% [70]. *D. salina* showed accumulation of C14:0, C16:0, C16:1, C16:2, C18:0, C18:1, C18:2 and C18:3 fatty acids. Biofuel yield from *Dunaliella salina* was found better than other commercial biofuel crops as depicted in TABLE 2. Microalgae *Dunaliella salina* has greater conversion efficiency of algal oil into biodiesel [71]. *D. salina* posses highest percentage of poly unsaturated fatty acids viz., 18:3 (30.26%) and 18:2 (13.24%) followed by mono unsaturated fatty acids like 16:4 (11.24%), 16:2 (3.0%), 16:3(1.16%) and saturated fatty acid such as 16:0 (18.20%), 14:0 (0.51%) [72].

Over the past years researchers are mainly focused on either over-expressing candidate molecules that play role in biosynthesis of fatty acid (e.g.-acetyl-CoA carboxylase) or knocking down genes that perform the role of oxidation of fatty acids (e.g.-acyl CoA oxidase, acyl CoA synthase, carnitineacyltransferase I, fatty acyl CoA dehydrogenase) [73]. ACS or Acetate-CoA ligase plays role in metabolizing acetate to form Acetyl CoA and Pyrophosphate. Algal cells grown in different oil-accumulating conditions showed that ACS, encoding a chloroplastic acetyl-CoA synthetase, is up-regulated at all conditions in *C. reinhardtii* and other chlorophytes, such as Dunaliella [74]. Over expression of this enzyme could yield higher lipid production.

International status of *Dunaliella salina* biofuel production

GC/MS study of *Dunaliella salina* was done for understanding the FAME(Fatty Acid Methyl Ester) profile. Many classes of FAMEs were detected through GC/MS analysis. The results prove that tetradecanoic acid and hexadecanoic acids are abundantly found in Dunaliella. Presence of other types of fatty acid methyl esters in *D. salina* such as docosanoic acid, eicosanoic acid, pentacosanoic acid, octadecanoic acid, undecanoic acid, dodecanoic acid, nonadecanoic acid was also observed. Selection of high-oil content strains and evaluating cost effective methods of harvesting, oil extraction and conversion of oil to biodiesel is essential for producing biodiesel from algae [75] Hexadecanoic acid(palmitic acid), Octadecanoic acid (stearic acid) the two most commonly found fatty acid in biodiesel constitutes up to 23.7% and 7.3% of total fatty acids in *D. salina*. Other saturated fatty acids composition comprise (FAME:%total) Docosanoic acid methyl ester:7.1%; Eicosanoic acid methyl ester: 4.6%; Pentacosanoic acid methyl ester: 5.5%; Hexadecanoic acid methyl ester :23.7%; Octadecanoic acid methyl ester :7.3%; Undecanoic acid methyl ester: 5.9%; Tetradecanoic acid methyl ester: 20.3%; Dodecanoic acid methyl ester :4.1%; Nonadecanoic acid methyl ester: 6.1% ;Hexadecanoic acid ethyl ester :7.9%. The highly saturated fatty acids offer very good cetane number and these types of fatty acids (e.g. stearic acid) are abundantly available in *D.salina* [76].

Biomass and lipid production in *D. salina* under influence of salinity

High salinity is accompanied by a positive impact in biomass and lipid addition of *D. salina*. In a research published by R A Ahmed et. Al [77]. in year 2017 the results showed that the highest biomass concentration (1231.66±1.26mgL^{-1}, lipid content (248.33mgL^{-1}) was found at 2M NaCl .This hike in lipid content at highest salt concentration was probably an adaptation to stress conditions; also, the percentage of total lipid, 22.28%, was seen at the highest salinity level, 2.5M. This proves the fact that salt stress significantly increases the percentage of lipids in *D. salina*, but it is noteworthy that along with decrease in overall biomass production of the culture, the overall lipid productivity also decreases. *Dunaliella* sp. when altered with media concentration 3 M NaCl to 2 M NaCl led to increase in lipid content from (220 and 280) to (350 and 430) g kg^{-1}whereas carbohydrate content jumped from 0.076 g^{-1} to 0.115 g^{-1}, carotenoids from (1.8 and 2.4) to (2.3 and 3.7) pg cell^{-1}, SOD (superoxide dismutase) activity from (46.6 and 61.8) to (71.6 and 79.4) U mg^{-1} proteins and TBARS(Thiobarbituric acid reactive substances) amount from (10.4 and 5.3) to (12.1 and 10.7) nmol mg^{-1} proteins, respectively [78].

In a study performed by Chen and coworkers The results concluded that presence of sodium azide increased lipid content and had no significant effect on cell biomass. Total lipid productivity and single cell lipid content under 50 μM sodium azide was enhanced by 10.4% and 21.7%.Further on combination of the treatment of 50 μM sodium azide and 2.5 M salt stress, both above mentioned parameters were 10% and 70.5% more than control, showing that

both these compounds synergistically effect the lipid accumulation in *D. tertiolecta* [78]. First genetic engineering attempt to raise microalgal lipid content (LC) was done by up-regulating the major initial steps of fatty acid synthesis via over expression of acetyl-CoA carboxylase (*ACCase*) and malic enzyme resulted in a 12% increase in LC. Thus increased lipid accumulation by over expression of relevant enzymes or intermediates is difficult process [79]. In another study cDNA of ACS(AMP-forming acetyl-CoA synthetase which acts as catalyst in generation of acetyl-CoA) from *Dunaliella tertiolecta* (DtACS) was isolated with RACEs. The full-length DtACS cDNA (GenBank: KT692941) was 2,464 bp with a putative ORF of 2,184 bp, which codes for 727 amino acids with an estimated molecular weight of 79.72 kDa. Further it was reported that lipid contents were exaggerated in *D. tertiolecta* beneath N deficiency condition, and cells cultivated in nitrogen-deficient medium accumulated large amounts of lipid by days three to five. During this study, it had been found that the transcription levels of DtACS were augmented under nitrogen-deficient cultivation, and therefore the highest transcription level of DtACS happened at the nitrogen-deficient treatment by day five. It can be a hypothesis that ACS activity could also be involved in lipid accumulation in *D. tertiolecta* [80].

Future prospective

Although many genes have been identified which are involved in lipid biosynthesis/oxidation but still there exist several enzymes whose function is yet to be deciphered. Systems biology approach where not only single enzyme or transcript based engineering rather pathway based alterations are a possibility of the future. Thus using current molecular approaches and latest advancements in life sciences would be a noteworthy step in fulfilling the needs of the future demand of fuels.

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TABLE 1: THE ADVANTAGES AND DISADVANTAGES OF TRANSFORMATION METHODS FOR *Dunaliella salina*

Transformation method	**Electroporation**	**Particle bombardment**	**Glass beads**	**LiAc/PEG**
Transformation rate	2 %	<1 %	5.9 %	7.21 %
Specialized equipment	Electroporation apparatus	Particle gun, Tefzel tube	Vortex mixer, glass beads	LiAc, PEG
Expenses	High	High	Low	Low
Repeatability	Good	Bad	Good	Good
Operation process	Simple and easy	Complex and difficulty	Simple and easy	Simple and easy
Specially used	Nuclear	Chloroplast	Nuclear	Nuclear
References	91	92	93	94

TABLE 2: BIOFUEL YIELD FROM COMMONLY AVAILABLE BIOFUEL CROPS

Crops	Gravimetric Biofuel yield expressed in (gram/1.5gram dw)	Percentage of Biofuel yield
Castor	0.501	33.4
Jatropha	0.933	62.2
White soy bean	0.568	37.8
Soy bean	0.141	9.4
Coconut	0.862	57.4
Red Groundnut	0.768	51.2
Dunaliella salina	1.0	66.6

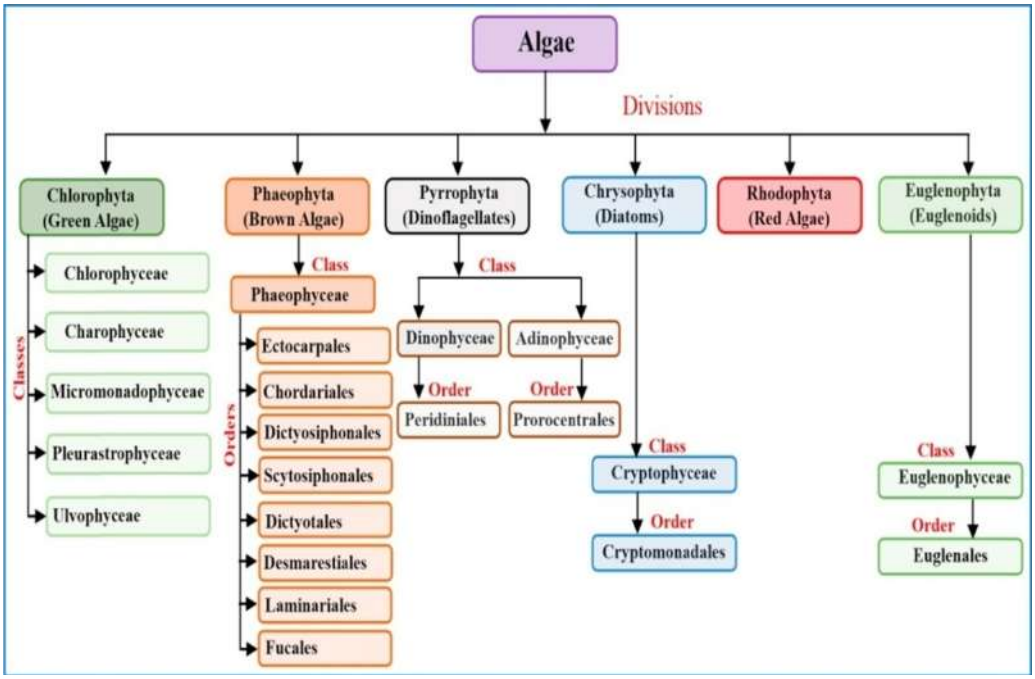

Figure 1: Main groups of Algae

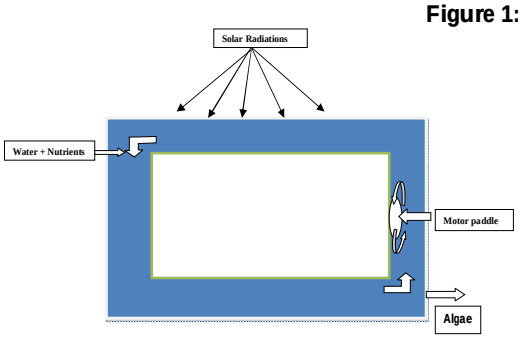

Figure 2: Open Type /Raceway Ponds

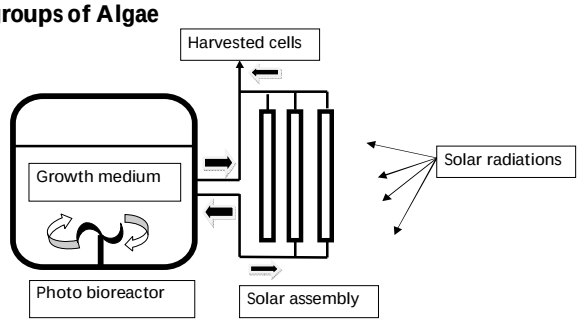

Figure 3: Closed type or Photobioreactor

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REVIEW ARTICLE

Plant Based Vaccines: A Review

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ABSTRACT

Plant-based vaccine technologies involve the integration of the desired genes encoding the antigen protein for specific disease into the genome of plant tissues by various methods. Agrobacterium-mediated gene transfer and transformation via genetically modified plant virus are the common methods that have been used to produce effective vaccines. Vaccine is a biological substance that is introduced into the body to prevent infection or to control disease due to certain pathogen which is disease causing organism such as a virus, bacteria or parasite. Vaccines are usually administered by needle injections (parenteral administration), and but some are given orally or even nasally (in the case of flu vaccine).A vaccine is inducing the body immune system and produce the antibodies action against the disease-causing microorganism. vaccinations can also prevent widespread of diseases in populations and therefore the side effect of vaccinations.

Keywords: Plant tissues, Vaccine, Disease, Immunity, Antigen, Pathogen.

INTRODUCTION[1]

- The attempt to produce vaccines in plants was made by Hiatt and coworkers in 1989.
- The concept of utilizing transgenic plants to produce and deliver subunit vaccines was introduced by Dr. Arntzen and his colleagues and proved that this concept can overwhelm the limitations in traditional vaccine production.
- The first subunit vaccine was produced by them in tobacco plants by expressing surface protein antigen of *Streptococcus mutants*.

- Vaccine is a biological substance that is introduced into the body to prevent infection or to control disease due to certain pathogen like virus, bacteria or parasite. Vaccines are usually administered by needle injections, but some are given orally or nasally. A vaccine can confer active immunity against a specific harmful agent by stimulating the immune system to attack the agent.
- Moreover, plant-based edible vaccines produced through this method are able to provide a needleless, convenient, and easy route of administration.
- Among the plants that have been commonly used as bioreactor are tobacco, potato, tomato, corn, and rice. To date, there are many transgenic plants that have been used to produce four different types of vaccines: bacterial vaccines, viral vaccines, parasite vaccines, and immune contraceptive vaccines
- Vaccines protect against many diseases. Examples include tetanus, diphtheria, mumps, measles, pertuss is (whooping cough), meningitis, and polio. Many of these infections can cause serious or life-threatening illnesses and may lead to life-long health problems. Because of vaccines, many of these illnesses are now rare.
- The administration of vaccines is named vaccination. Vaccination is that the best method of preventing infectious diseases. Vaccination is that the most successful medical approach to disease prevention and control. In the future, vaccines have the potential to be used not only against infectious diseases but also for cancer as a preventive and treatment tool.

Production of Plant Based Vaccines:[2]

- Plant-based vaccine production mainly involves the integration of transgene into the plant cells. The target sequence of the selected antigen is integrated with the vector before being transferred into the expression system. The transgene can then be expressed in the plants either through a stable transformation system or through transient transformation system, depending on the location where the transgene has been inserted in the cells.Stable transformation system can be achieved through nuclear or plastid integration.
- It is called stable or permanent due to the permanent changes occurring in recipient cells' genetics as the target transgene is integrated into the genome of host plant cells. Biolistic and genetically modified *Agrobacterium* strain can lead to the formation of stable transfection.
- However, as *Agrobacterium tumefaciens* is not infecting many plant species naturally, it limits the application of *Agrobacterium* strain for stable transformation of the desired gene. Generally, stably transgenic plant cells produce a lower amount of subunit antigen, in the range of 0.01 to 0.30% of total soluble plant protein.On the other hand, transient transformation system involves the production of desired protein or antigen soon after the heterologous gene resides transiently in the host cells.
- The transgene is not incorporated into the genome of the plant cells. In this plant expression system, the regeneration of whole plant is not required and the frequency of its occurrence is higher. These characteristics overcome the pitfalls related to the stable integration.
- Two most commonly used methods that would achieve transient expression of a desired protein in plants are the *Agrobacterium*-mediated transformation of genetically modified plant virus and particle bombardment.

Aim and Objectives

The main aim of the present work is to review on recent advancement of vaccines and the possible modification for the future development of vaccines.

Objectives

1. Rapidly increase the immunization coverage.
2. Reduction of pressure on the health care system.
3. To save lives, prevent premature death and disability
4. Reduce health sector costs for hospital care.
5. Disease elimination.

Types of Vaccine:[3]

- There are several different types of vaccines. Vaccines may be viral (live or inactivated), viral vector, subunit (protein or polysaccharide) or nucleic acid (DNA or RNA). Combination vaccines may include inactivated, protein-basedor protein-conjugated polysaccharide vaccine components.
- There has been an increased focus on vaccine development using the viral-vector and nucleic-acid based platforms since the appearance of the SARS-CoV-2 virus and COVID-19 disease in late 2019.

1. live Attenuated
2. Inactivated
3. Toxoid
4. Subunit
5. Conjugate
6. Heterotypic
7. Viral vector
8. Nucleic acid-based vaccines

Live Attenuated Vaccine:[4]

- Live attenuated vaccines contain whole bacteria or viruses have been "weakened" (attenuated).so, it can replicate in the body several times and generate an immune response without causing the disease, because these vaccines are similar to the natural infection that they help prevent, they create a strong and long-lasting immune response. Just 1 or 2 doses of most live vaccines can give you a lifetime of protection against a germ and the disease it causes.
- When the vaccine virus is given to a person, it'll be unable to cause illness, but will still provoke an immune reaction which will protect against future infection.

o e.g., The BCG vaccine contains live weakened tuberculosis bacteria.

Killed or Inactivated Vaccines: [5-6-7]

- Inactivated vaccines contain whole bacteria or viruses have been killed. so, they cannot replicate. However, they do not always create such a strong or long-lasting immune response as live attenuated vaccines. inactivated vaccines are prepared by using heat or chemicals like formaldehyde or formalin.
- This destroys the pathogen's ability to duplicate, but keeps it "intact" in order that the system can still recognize it.

Toxoids: [8-9]

- Immunizations for this type of pathogen are often made by inactivating the toxin that causes disease symptoms. like organisms or viruses utilized in killed or inactivated vaccines, this may be done via treatment with a chemical like formalin, or by using heat or other methods.
- Immunizations created using inactivated toxins are called toxoids. Toxoids can actually be considered killed or inactivated vaccines, but are sometimes given their own category that they contain an inactivated toxin, and not an inactivated form of bacteria.

Subunit and Conjugate:[10]

- The vaccines contain proteins or sugars derived from the disease-causing organisms. Both subunit and conjugate vaccines contain only pieces of the pathogens they protect against.
- Subunit vaccines use only part of a target pathogen to provoke a response from the immune system. This may be done by isolating a specific protein from a pathogen and presenting it as an antigen on its own.
    - o e.g., The acellular pertussis vaccine and influenza vaccine are examples of subunit vaccines.

Conjugate:[11]

- Conjugate vaccines are designed from parts of the bacterial coat. However, these parts won't produce an efficient immune response when presented alone. Hence, they're combined with a carrier protein. These carrier

proteins are chemically linked to the bacterial coat derivatives. They generate a stronger response and may protect the body against future infections.

- e.g., Vaccines against pneumococcal bacteria used in children

Viral Vector:[12-13]

- Viral vector-based vaccines differ from most conventional vaccines therein they don't actually contain antigens, but rather use the body's own cells to supply them. By infecting cells and instructing them to make large amounts of antigen, which then trigger an immune response, the vaccine mimics what happens during natural infection with certain pathogens - especially viruses.
- e.g., of a viral vector vaccine is the rVSV-ZEBOV vaccine against Ebola
- There are two main sorts of viral vector-based vaccines. Non-replicating vector vaccines are unable to form new viral particles; they only produce the vaccine antigen. Replicating vector vaccines also produce new viral particles within the cells they infect, which then continue to infect new cells which will also make the vaccine antigen.

Nucleic Acid-Based Vaccines:[14]

- At present, different types of nucleic-acid vaccines are in developmental, pre-clinical and clinical evaluation phases, e.g., for prevention of human immunodeficiency virus (HIV), influenza and malaria diseases and treat some cancers.
- Nucleic acid vaccines use genetic material from a disease-causing virus or bacterium to stimulate an immune response against it.
- Depending on the vaccine, the genetic material could be DNA or RNA; in both cases it provides the instructions for making a specific protein from the pathogen.
- Nucleic acid vaccines work in a different way to other vaccines in that they do not supply the protein antigen to the body. Instead, they provide the genetic instructions of the antigen to cells in the body and in turn the cells produce the antigen, which stimulates an immune response. Nucleic acid vaccines are quick and easy to develop.

Vaccines Discovered

1796-Cowpox Vaccine:

Small pox is acute contagious viral disease. It was contagious means, it spread from one person to another. it was a serious infectious disease caused by the variola virus.

Symptoms of Small pox.

1. Fever
2. Overall discomfort.
3. Headache
4. Severe fatigue
5. Severe back pain
6. Vomiting

Diagnosis: [15-16]

1. Febrile prodrome occurring 1 to 4 days before rash onset.
2. Fever ≥101°F (38.3°C).
3. Smallpox can be diagnosed based on the patient's clinical signs and symptoms.
4. The disease can be definitively diagnosed by isolation of the virus from the blood or lesions,

- Dr. Edward Jenner collected bits of cowpox pustule the animal variant of smallpox and scratched it into the arm of an 8-year-old boy.
- Cowpox is a disease caused by the cowpox virus. The virus is transferable between species, like from cat to human. The transferral of the disease was first observed in dairymaids who touched the udders of infected cows and consequently developed the signature pustules on their hands.

- Cowpox is commonly found in animals. the highly contagious and sometimes deadly smallpox disease. The cowpox vaccinations proved so successful, that in 1980.Once vaccinated, a patient develops antibodies that make them resistant to cowpox, but they also develop immunity to the variola virus, or smallpox virus.
- Smallpox affected all levels of society. In the 18th century in Europe, 400,000 people died annually of smallpox. The case-fatality rate varied from 20% to 60%.The case-fatality rate in infants was even higher, approaching 80% in London and 98% in Berlin during the late 1800s.

1885-Rabies Vaccine[17]

- Rabies is a viral infection that is spread mainly through the bite of an infected animal.
- Rabies virus causes rabies. If left untreated, it is usually fatal. Viruses can affect the body in two ways: directly entering the peripheral nervous system (PNS) and traveling to the brain. The virus is spread via the saliva of an infected animal.
- Rabies, also known as hydrophobia. The virus multiplies rapidly in the brain. This activity can cause severe inflammation of the brain and spinal cord, after which people will quickly deteriorate and die.
- By using a mixture of both mature plant and phytoembryonic tinctures, you can support your dog throughout the vaccination process.
- Phyto embryonic tinctures are sold commercially as gemmotherapies. They are made from the Phyto embryonic stem cells of either plant buds, young shoots, rootlets, or young barks mixed with alcohol, glycerin, and water. Most commercial gemmotherapy preparations in the United States are diluted to a 10x (diluted ten times) potency making them compatible with both mature plant tinctures and homeopathic preparations.

Symptoms

- Fever.
- Headache.
- Nausea.
- Vomiting.
- Anxiety.

Diagnosis[18-19]

1. Direct fluorescent antibody (DFA) test
2. Fluorescent antibody test (FAT),
3. The direct fluorescent antibody (DFA) test is used to diagnose rabies and looks for the presence of rabies virus antigens in brain tissue.

- Pasteur has successfully developed a vaccine against rabies. Pasteur used the equivalent method he developed for the anthrax vaccine.
- There are two ways to use the rabies vaccine. Rabies vaccines are used for people who come into contact with (for example, biting, scratching, or licking) animals that are known or believed to have rabies. This is called post-exposure prevention. Rabies vaccine can also be provided early to people at high risk of infection with rabies virus.
- These people include veterinarians, animal keepers, or travelers who will stay in a country with a high rabies infection rate for a month, as well as people who live, work, or vacation in wild areas of countries where they may return. Contact with wild animals. This is called pre-exposure prevention.
- Worldwide, approximately 59,000 people die each year from rabies transmitted by dogs.
- In Asia, due to rabies transmitted by dogs, an estimated 35,172 deaths per year (59.6% of global deaths).
- In Africa, the estimated number of human deaths from rabies reported annually is 21,476 (representing 36.4% of global deaths). In Asia, India is the country with the highest number of human deaths from rabies (59.9%) and the world (35%)
- After India and China are the other countries most affected by rabies. Even after huge economic investments, rabies remains a major health problem in Asian and African countries.

1938 - Tetanus Vaccine [20]

- Tetanus is an infection caused by a bacterium called Clostridium tetani. the bacteria enter the body, to produce a poison that causes painful muscle contraction. Another name for tetanus is "lockjaw". It usually causes a person's neck and jaw muscles to lock up, making it difficult to open the mouth or swallow.

Symptoms

1. Painful muscle stiffness all over the body.
2. Trouble swallowing.
3. Headache.
4. Fever and sweating.
5. Changes in blood pressure and fast heart rate.

Diagnosis [21]

1. Physical exam,
2. Medical history
3. Vaccination history

- The first active tetanus toxoid was discovered in 1924. A simpler adsorption version of the vaccine, made in 1938, proved successful when it failed to prevent tetanus in the armed forces during World War II.
- Tetanus vaccine, also known as tetanus toxoid (TT), canprevent tetanus. Five doses are recommended for children and six doses are recommended during puberty.
- Almost everyone becomes immunized first after 3 doses, but boosters are recommended every 10 years to maintain immunity.
- The type of vaccination against this disease is called artificial acquired immunity. This type of immunity is generated when a dead or weakened disease enters the body and causes an immune response that involves antibody assembly. This is beneficial for the system to recognize antigens and produce antibodies more quickly when the disease enters the body.
- About 59,000 people died in 2013, down from 356,000 in 1990. Mortality rates in the United States were 91% in 1947, 2131% in 1982 to 1990, 11% in 1995 to 1997, and 18% in 1998 to 2000. Current statistics show that the mortality rate for mild and moderate tetanus is about 6%. In severe tetanus cases, it is as much as 60%.
- The mortality rate in the United States from systemic tetanus is 30% overall, 52% in patients over 60 years of age, and 13% in patients younger than 60 years of age. The mortality rate for people over 60 (40%) is much higher than for people over the age of 2059 (8%). From 1998 to 2000, 75% of our deaths were patients aged 60 years or older.

1955-Polio Vaccine[22]

- Polio is a disabling and life-threatening disease caused by the polio virus. The virus can spread from person to person, infecting the person's spinal cord, causing paralysis and weakness.
- Polio is caused by three types of polio viruses. There is a lot to be spread by face-to-face contact with an infected person. It can also be caused by eating and drinking contaminated food or water. Polio is visible in infants and occurs in conditions of poor hygiene.

Symptoms

1. Fatigue
2. Fever
3. Headache
4. Pain in the arms and legs

Diagnosis[23]

1. Stool specimens
2. Sample of throat secretions
3. Colourless fluid that surrounds your brain and spinal cord (cerebrospinal fluid) is checked for poliovirus.

- The polio vaccine is used for polio. Two types are used: inactivated poliovirus (IPV) given by injection and attenuated poliovirus (OPV) given by mouth. The World Health Organization (WHO) recommends that all children should fully vaccinated against polio.
- The number of annual reported cases in which polio has been eradicated from most of the places. The inactivated polio vaccine is very safe. The injection site may become slightly red or painful.
- The first successful polio vaccine demonstration was in 1950 by Hilary Koprowski using a live attenuated virus to isolate a beverage.
- More than 2,000 deaths occurred in New York City alone, which had more than 27,000 cases and more than 6,000 deaths due to polio in the United States that year.
- Two vaccines are used worldwide to eradicate polio. Salk vaccine or inactivated vaccine (IPV) consists of an injected dose of inactivated poliovirus. In 1954, the vaccine was tested for its ability to stop polio. Its field trials were the most important medical experiments in history.
- In 1955, it was chosen to be used by all of us. By 1957, the annual number of polio cases in the United States had declined from about 58,000 at peak to 5,600.

1967-Mumps Vaccine:[24]

- Mumps is an infectious disease caused by viruses and inflammation of the salivary glands, especially the parotid glands. It is spread by sneezing or coughing due to infection.

Symptoms

1. Discomfort in the salivary glands.
2. Difficulty chewing.
3. Fever.
4. Headache.
5. Muscle aches.
6. Tiredness.

Diagnosis[25]

1. Blood or urine test.
2. Cerebrospinal fluid

- Mumps is caused by an infectious disease. Mumps usually begins with a fever, headache, muscle aches, fatigue, and loss of appetite. After that, most people develop swelling of the salivary glands.
- Although mumps infection in children was not considered a serious public health problem. The first mumps vaccine was approved in 1948. It was developed from an inactivated virus and has only a short-term effect.
- Mumps can be prevented by MMR vaccine. It protects against three diseases like measles, mumps and rubella. The CDC recommends giving children two doses of the MMR vaccine. The first dose is at 12-15 months of age, the second dose at 4-6 years of age. Teenagers and adults are also getting the MMR vaccine so far.
- MMR vaccine is very safe and effective. The mumps component of the MMR vaccine is effective in about 88%.
- Mumps spreads all over the world. Without mumps vaccination, 100-1,000 cases occur per 100,000 people each year. That is, it infects 0.1% to 1.0% of the population each year. The incidence peaks every 2 to 5 years and is highest in children aged 5 to 9 years.

1996-Chickenpox Vaccine:[26]

Highly contagious infectious disease, usually in children, caused by the varicella zoster virus of the genus Varicella. Chickenpox is spread by respiratory secretions or by contact with broken skin.

Symptoms

1. Fever, feeling tired, headache.
2. A stomach-ache that lasts for one or two days.
3. A skin rash that is very itchy and looks like many small blisters.

Diagnosis [27]

1. Polymerase chain reaction (PCR)
2. Visual examination.
3. The use of polymerase chain reaction (PCR) to detect VZV in skin lesions (vesicles, scabs, macular lesions).

- The research team of American vaccinator Maurice Hilleman at Merck invented the chickenpox vaccine in 1981.
- Japan was one of the first countries to vaccinate against chickenpox. The vaccine developed by the Hilleman and first licensed in the United States in 1995. One dose of vaccine prevents 95% of moderate illnesses and 100% of serious illnesses.
- Approximately 400,000 cases occur annually in the United States, mostly children, and generally 10,500-13,000 hospitalizations (range, 8,000-18,000) occur annually, with 100-150 cases Dead. Most children were infected, but most deaths were adults.

2020-Covid 19 Vaccine: [28-29]

- At present, specific therapies for COVID-19 are not well established, being certain only that the immune system plays a decisive role in the initiation and progression of the disease. Plants have given and continue to give compounds with great efficiency and low toxicity, some of them being a starting point for extremely effective synthetic substances.
- Although herbal remedies are used mainly for preventive purposes, there are also guidelines issued by some countries that indicate the use of traditional remedies for different stages of COVID-19 disease.Europe has a long and strong tradition of using medicinal plants for therapeutic purposes, but clinical trials for this type of approach are scarce, compared to Asia. In this regard, a bridge between tradition and science, would have a strong impact on the capacity for prevention and treatment of COVID-19.
- Since the disease started in China, a place with strong roots in traditional medicine, it is understandable to approach natural therapy in this case as well. Although herbal remedies are used mainly for disease prevention, there are also guidelines issued by the Chinese and Korean ministries of health that indicate the use of traditional remedies for different stages of the disease. However, detailed clinical trials are needed to determine the effectiveness of these remedies. On the other hand, plants have given and continue to give compounds with great efficiency, some of them being a starting point for easy to-obtain and highly effective synthetic substances. An example is chloroquine, a structural analog of quinine, originally extracted from the bark of cinchona trees, which has been shown to be effective in treating COVID-19.
- People may be infected when they breathe in aerosols or droplets containing the virus or directly touch the eyes, nose or mouth. Corona viruses are zoonotic, which means they can spread between animals and people. The virus that causes COVID19 belongs to a family of viruses called Coronaviridae.

Symptoms

1. Fever, cough and shortness of breath
2. Loss of taste or smell
3. Sore throat

Diagnosis [30]

1. Rapid diagnostic tests (RDT)
2. Swab Test
3. CT scans
4. Throat (throat swab) or saliva.
5. The polymerase chain reaction (PCR) test

- In humans, corona viruses can cause respiratory infections, ranging from mild to fatal. Current evidence suggests that the virus spreads, usually within a meter, primarily between people in close contact with each other. People could also be infected once they inhale droplets containing the virus or directly touching the nose or mouth. The virus that causes COVID19 belongs to a family of viruses called Corona viridae
- The benefit of preventing the spread is to understand the COVID19 virus, the diseases it causes and how it spreads, Protection etc. Wash your hands or use alcohol-based disinfectants. Covaxin is a COVID19 vaccine based on an inactivated virus, jointly developed by Bharat Biotech and the Indian Medical Research Council.

- In July 2021, Bharat Biotech reported that the vaccine has an effective rate of 64% for asymptomatic cases and 78% for symptomatic cases, The effective rate for symptomatic cases is 93% for severe COVID19 infection, and 65% for Delta variants. On December 6, 2020, Bharat Biotech submitted an application requesting emergency use authorization.
- On January 2, 2021, the Central Pharmaceutical Standards Control Organization (CDSCO) recommended the license, and was approved the next day. As of August 19, 2021, 209,201,939 confirmed cases of COVID19 have been reported to WHO globally, including 4,390,467 deaths. As of August 18, 2021, 4,543,716,443 doses of vaccine had been vaccinated

CONCLUSION

Studies have shown that the benefits of vaccination outweigh the risks, because vaccines can prevent serious illness and disease in people, and vaccination can also prevent the widespread spread of disease in the population. Therefore, although the side effects of vaccination are sometimes serious, they are very rare. The advantage of vaccination is to offset the risk, and the vaccine does that and has eliminated many diseases. For centuries, vaccination has played an important role. People began using Chinese, Turkish and Asian vaccination techniques dating back to 1000 AD. One of the main objectives is to strengthen the scientific basis for the evolution of vaccines and public health care and disease prevention. Although it is generally believed that infectious diseases will be eliminated in the 20th century, in the past 20 years, new and re-emerging infections have appeared in different parts of the world, and their incidence is likely to spread in the future.

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Table No:1-US recommended types of vaccines

Vaccine type	**Vaccines of this type on U.S. Recommended**
Live/attenuated	Measles, mumps, rubella (MMR combined vaccine) Varicella (chickenpox) Influenza (nasal spray) Rotavirus
Inactivated/Killed	Polio (IPV) Hepatitis A
Toxoid (inactivated toxin)	Diphtheria, tetanus (part of DTaP combined immunization)
Subunit/conjugate	Hepatitis B Influenza (injection) Haemophilus influenza type b (Hib) Pertussis (part of DTaP combined immunization) Pneumococcal Meningococcal
Live, attenuated	Zoster (shingles) Yellow fever
Inactivated / killed	Rabies
Subunit/conjugate	Human papillomavirus

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RESEARCH ARTICLE

Fuzzy Mathematical Modeling of Dynamical System

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ABSTRACT

Fuzzy differential equations play an important role in the modelling of dynamic systems in economics and engineering. Modeling roles are important as most problems in nature are obscure and uncertain. In this paper, we intend to introduce Euler's method for solving fuzzy dynamical Modeling (FDM) under generalized differentiability. The approximate solution is illustrated by numerical examples, including graphs for linear first order fuzzy differential equations to show the advantage of our proposed method.

Keywords: Fuzzy Dynamical Modeling**,** Fuzzy Number, Generalized differentiability, Fuzzy initial value problem, Fuzzy Euler's method.

INTRODUCTION

A dynamic system is one that changes over time. A mathematical-dynamic system consists of the space of states of the system together with a rule called dynamics to determine the state that corresponds to a certain future point in time. In a given present state, once the dynamics have been given, it is the task of the mathematical theory of dynamic systems to study the long-term pattern of state change. To develop a Fuzzy Mathematical Model and assess its performance in Naval System by applying the simulation of prediction to Design, tested, and integrated. To access Dynamic modeling problems using Fuzzy Differential Equations. Computer algorithm for Simulation of Fuzzy Differential Equation is developed. To implement an algorithm and study the behavior of real arm and compare with the simulation result obtained from the algorithms. Mathematical model is an effective tool to understand the dynamics of disease to identify the influential parameters in spreading the disease and to propose strategies to control the disease. From medical engineering point of view, mathematical modelling approach is one of the key tool

in order to handle the infectious diseases. Their applications are found in areas of physical and medical sciences. Kermack, Mc. Kendrick first formulated the mathematical model based on three ordinary differential equations which presently is called the SIR model [1].Few researchers used fractional order derivative with Mittag – Leffer function as a non-singular kernel type [3] and caputo derivative [4 – 6] to model transmission of COVID – 19.Kamal et al.[4] establish some necessary conditions for existence of atleast one solution to model under investigation and its uniqueness. Muhammad A was et al. [6] considered the real cases of coronavirus in China from January 11, 2020 to April 9, 2020 and estimated the basic reproduction number as $R_0 \approx 4.95$. Khan et al. formulated a new mathematical model for the dynamics of COVID-19 with quarantine and isolation[7]. Sindu Devi et.al.,[8] discussed about the temperature of the soup with various changes in time using Newton's law of cooling. Allahviranloo et al.[2] introduced the fuzzy generalized Euler's method as an application of the generalized Taylor expansion and demonstrated how to use it to solve the fuzzy fractional differential equation by presenting several theorems about the generalized Euler's method's consistency, convergence, and stability. Wan Suhana [10] Wan Daud and colleagues used the fuzzy Euler method to apply fuzzy differential equations to a tumor-immune interaction system with fuzzy beginning values. Babolian et al[11] introduced the Euler approach for addressing one-dimensional fuzzy differential inclusions based on the numerical results. The Euler technique can be used to approximate a fuzzy reachable set with complete error analysis.In this paper, we introduce Euler's method for solving first order fuzzy dynamical modelling . We give some numerical examples based on the proposed method and finally we give conclusion ofthis study.

Preliminaries

This section contains some basic definitions which is very useful throughout this paper.

Definition 2.1. A fuzzy set $\tilde{a}$ definedon the set of real numbers R is said to bea fuzzy number if its membership function $\tilde{a}: R \to [0,1]$has the following:

i. $\tilde{a}$is convex, i.e, $\tilde{a}\{\lambda x_1 + (1-\lambda)x_2 \geq \min\{\tilde{a}(x_1), \bar{a}(x_2)\}$, for all $x_1, x_2 \in R$ and $\lambda \in [0,1]$
ii. $\tilde{a}$is normal i.e., there exists an $x \in R$ such that $\tilde{a}(x) = 1$
iii. $\tilde{a}$is piecewise continuous

Definition 2.2. A triangular fuzzynumber is denoted as $\tilde{a} = (a_1, a_2, a_3)$andis defined by the membership function

$$\tilde{a} = \begin{cases} 0, & x \leq q, \\ \dfrac{x - a_1}{a_2 - a_1}, & a_1 \leq x \leq a_2, \\ \dfrac{a_3 - x}{a_3 - a_2}, & a_2 \leq x \leq a_3, \\ 0, & x \geq a_3. \end{cases}$$

Fuzzy Derivative

Definition 2.3. [Hukugara Derivative] Consider a fuzzy mapping $F: (a,b) \to R$ and $t_0 \in (a,b)$. We say that F is differentiable at $t_0 \in (a,b)$if there existsan element $F'(t_0)\, R$ such that for all$h$ > 0sufficiently small $\exists F(t_0 + h) \ominus F(t_0), F(t_0) \ominus F(t_0 - h)$and the limits(in the metric D)

$$\lim_{h \to 0_+} \frac{F(t_0 + h) \ominus F(t_0)}{h} = \lim_{h \to 0_-} \frac{F(t_0) \ominus F(t_0 - h)}{h}$$

exists and are equal to $F'(t_0)$.

Fuzzy Initial Value Problem

An initial value problem is a system of ordinary differential equations together with the initial conditions. Consider a function of n^{th} order fuzzy differential equations with initial conditions are

$$\tilde{y}^n(t) = \tilde{f}(t, y(t), y'(t), \dots, y^{n-1}(t)$$
$$\tilde{y}(t_0) = y_0, \dots, \tilde{y}^{n-1}(t_0) = y_0.$$

By using Extension principle, the membership functions are

$$[\tilde{f}(t,\tilde{y})]^{\alpha} = \tilde{f}(t,[\tilde{y}]^{\alpha}) = \tilde{f}\left(t,\left[\underline{y}_{\alpha},\overline{y}_{\alpha}\right]\right) = \left(\min \tilde{f}\left(t,\left[\underline{y}_{\alpha},\overline{y}_{\alpha}\right]\right),\max \tilde{f}\left(t,\left[\underline{y}_{\alpha},\overline{y}_{\alpha}\right]\right)\right)$$

here $y(t)$ is an unknown fuzzy function of crisp variable t and $f:[0,T]*R_F \to R_F$ is continuous, also $y'(t)$ is the generalized Hukuhara derivative of $y(t)$ such that the set of switching points is finite.

Proposed Method

The general solution of exact and approximate at $t_n, 0 \le n \le N$ are denoted by

$$[Y(t_n)]_{\alpha} = [\underline{Y}(t_n;\alpha),\overline{Y}(t_n;\alpha)],[y(t_n)]_{\alpha} = [\underline{y}(t_n;\alpha),\overline{y}(t_n;\alpha)]$$

First we are going to approximate $y'(t)$ in three Euler – based solution method by using the concept of generalized differentiability.

Euler's method

we calculate Euler's method as follows

$$\underline{y}_{n+1} = \min\{((y + hf(t,\underline{y}))/\, y \in [\underline{y}_n{}^{\alpha},\overline{y}_n{}^{\alpha}]$$

$$\overline{y}_{n+1} = \max\{((y + hf(t,\overline{y}))/\, y \in [\underline{y}_n{}^{\alpha},\overline{y}_n{}^{\alpha}]$$

Improved Euler's method

we obtain

$$\underline{y}_{n+1} - \underline{y}_n = \frac{h}{2}[f(t_n,\underline{y}(t_n;\alpha)] + f(t_{n+1},\underline{y}(t_{n+1};\alpha)]$$

$$\overline{y}_{n+1} - \overline{y}_n = \frac{h}{2}[f(t_n,\overline{y}(t_n;\alpha)] + f(t_{n+1},\overline{y}(t_{n+1};\alpha)]$$

Modified Euler's method

The Modified Euler's method can be written as follows.

Then we have

$$\underline{y}(t_{n+1};\alpha) = \underline{y}(t_n;\alpha) + \frac{h}{2}F\left[t_n,\underline{y}(t_n;\alpha);\overline{y}(t_n;\alpha)\right] +$$

$$\frac{h}{2}F\left[t_{n+1},\underline{y}(t_n;\alpha) + hF\left[t_n,\underline{y}(t_n;\alpha),\overline{y}(t_n;\alpha)\right],\overline{y}(t_n;\alpha) + hG\left[t_n,\underline{y}(t_n;\alpha),\overline{y}(t_n;\alpha)\right]\right]$$

$$\overline{y}(t_{n+1};\alpha) = \overline{y}(t_n;\alpha) + \frac{h}{2}G\left[t_n,\underline{y}(t_n;\alpha);\overline{y}(t_n;\alpha)\right] +$$

$$\frac{h}{2}G\left[t_{n+1},\underline{y}(t_n;\alpha) + hF\left[t_n,\underline{y}(t_n;\alpha),\overline{y}(t_n;\alpha)\right],\overline{y}(t_n;\alpha) + hG\left[t_n,\underline{y}(t_n;\alpha),\overline{y}(t_n;\alpha)\right]\right]$$

when n = 0,1,2,……..,N-1 To solve minimum and maximum problems, we adopt a computational method.

Numerical Example

Example 4.1

Consider the fuzzy initial value problem,

$$y'(t) = y(t), t \in [0,1] with$$

$$y(0) = (0.75 + 0.25r, 1.2 - 0.2r)$$

where $0 \le r \le 1$

Solution :

The exact solution is given by

$$\underline{y}(t:r) = \underline{y}(t:r)e^t \text{ and } \overline{y}(t:r) = \overline{y}(t:r)e^t$$

Then at t = 1,

$$y(1:r) = [(0.75 + 0.25r)e, (1.2 - 0.2r)e], 0 \le r \le 1.$$

CONCLUSION

In this paper, we have solved the first order linear generalized fuzzy differential equations by fuzzy Euler's method involving triangular fuzzy numbers. The proposed work emphasis the use of derivative with an aim to let reader witness the application of derivative to solve real life problem. Engineer manage to unravel their problems and resolve how to increase the speed with low fuel consumption and also we can find smooth and efficient running of the system. The simulation of the dynamic models provide higher level of process analysis. The models are designed to capture structural changes and characteristics of ecosystem.

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Table 1. Numerical Example

α	Simple		Improved		Modified		Exact	
	$\underline{y}$	$\overline{y}$	$\underline{y}$	$\overline{y}$	$\underline{y}$	$\overline{y}$	$\underline{y}$	$\overline{y}$
0.1	2.01015	3.060616	2.103413	3.202615	2.103413	3.202615	2.106669	3.207573
0.2	2.074994	3.008741	2.171265	3.148334	2.171265	3.148334	2.174626	3.153207
0.3	2.139837	2.956866	2.239117	3.094052	2.239117	3.094052	2.242583	3.098842
0.4	2.204681	2.904992	2.306969	3.039771	2.306969	3.039771	2.31054	3.044476
0.5	2.269525	2.853117	2.374821	2.985489	2.374821	2.985489	2.378497	2.99011
0.6	2.334368	2.801242	2.442672	2.931207	2.442672	2.931207	2.446454	2.935745
0.7	2.339212	2.749367	2.510525	2.876926	2.510525	2.876926	2.514411	2.881379
0.8	2.464056	2.697492	2.578377	2.822644	2.578377	2.822644	2.582368	2.827013
0.9	2.528899	2.645617	2.646228	2.768362	2.646228	2.768362	2.650325	2.772648
1	2.593743	2.593743	2.714081	2.714081	2.714081	2.714081	2.718282	2.718282

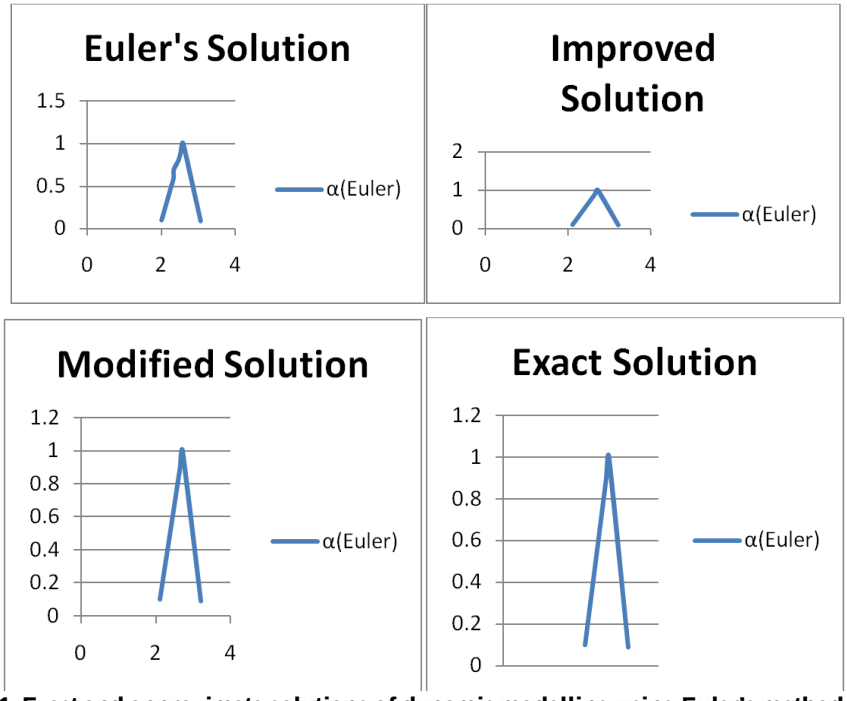

Figure1: Exact and approximate solutions of dynamic modelling using Euler's methods at t=1

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RESEARCH ARTICLE

The GC MS Study of One Ayurvedic Formulation, Shaddharana Churnam

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ABSTRACT

The GC MS analysis of one Ayurvedic formulation, Shaddharanacurnam was undertaken to have knowledge of the biomolecules present in it. The medicine was procured from standard Ayurvedic vendor at Chennai and was subjected to GC MS analysis after following the standard procedure. It was found that there are some molecules such as Cyclobutane-1,1-dicarboxamide, N,N'-di-benzoyloxy-, Hexadecanoic acid, methyl ester, n-Hexadecanoic acid, 12,15-Octadecadienoic acid, methyl ester, 9,12-Octadecadienoic acid (Z,Z)-, 15-Hydroxypentadecanoic acid, Decanedioic acid, bis(2-ethylhexyl) ester, .gamma.-Sitosterol etc. which have medicinal roles supportive of the role of Shaddharanachurnam in

curing diseases for which it is prescribed. Shaddharanachurnam does contain molecules with medicinal properties that augur well with the medicine.

Keywords: Shaddharanachurnam, GC MS, Ayurvedic, Hexadecanoic acid, methyl ester, n-Hexadecanoic acid, .gamma.-Sitosterol

INTRODUCTION

Ayurvedic, Sidhha and other forms of alternative and complementary medicines have not been tested and verified for their medicinal roles although they are in vogue since time immemorial. This lack of authentication and standardization has put them in the back bench of medicinal practice. There is an imperative need to bring this knowledge to light. This has become all the more important in the present world health scenario. Some work in this regard is pouring in and much more need be done.[1-29]The present study deals with the GC MS analysis of one Ayurvedic formulation, Shaddharanachurnam. This medicine is prescribed for Rheumatic complaints, skin diseases, piles, diabetes, flatulence, rheumatoid arthritis, gall stones and obesity. It is made of 6 ingredients as mentioned below:

Chitraka (*Plumbago zeylanica*), Indrayava (*Holarrhena antidysenterica*), Patha (*Cyclea peltata*), Katuka (*Picrorhiza kurroa*), Ativisha (*Aconitum heterophyllum*) and Abhaya (*Terminalia chebula*). These ingredients are separately powdered and mixed in equal quantities to prepare this medicine. The reference of this medicine is found in Bhaishajyaratnavali Vatavyadhiadhikara 26: 9-10.The manufacturers of this medicine are Ashoka pharmaceuticals, Arya Vaidya Sala Kottakkal, Arya Vaidya Pharmacy, Sitaram Ayurveda Pharmacy, Nagarjuna Ayurvedic Group among others. The dosage of the medicine is ½ to 1 teaspoon along with gomutra (cow urine) or warm water, twice daily before or after food as directed by physician. Tablets of this medicine are also available and the dose is 1 or 2 tablets along with water or as directed by the physician.

MATERIALS AND METHODS

Shaddharana churnam was obtained from standard Ayurvedic vendor at Chennai and was subjected to GC MS analysis by standard procedure.

Instrument

Gas chromatography (Agilent: GC: (G3440A) 7890A. MS MS: 7000 Triple Quad GCMS,) was equipped with Mass spectrometry detector.

Sample Preparation

100 micro lit sample Dissolved in 1 ml of suitable solvents. The solution stirred vigorously using vortex stirrer for 10 seconds. The clear extract was determined using gas-chromatography for analysis.

GC-MS protocol

The GC MS Column consisted of DB5 MS (30mm×0.25mm ID ×0.25 μm , composed of 5% phenyl 95% methyl poly siloxane), Electron impact mode at 70 eV; Helium (99.999%) was used as carrier gas at a Constant flow of 1ml/min Injector temperature 280 °C; Auxilary Temperature : 290°C Ion-source temperature 280 °C. The oven Temperature was programmed from 50 °C (isothermal for 1.0 min), with an increase of 40°C/min, to 170°C C (isothermal for 4.0 min), then 10°C/min to 310°C (isothermal for 10min) fragments from 45 to 450 Da. Total GC running time is 32.02 min. The compounds are identified by GC-MS Library (NIST & WILEY).

RESULTS AND DISCUSSION

The GC MS profile of Shaddharana churnam is represented in Figure 1. Table1 indicates the retentions values, types of possible compound, their molecular formulae, molecular mass, peak area and their medicinal roles of each compound as shown in the GC MS profile of Shaddharana churnam. The identification of metabolites was accomplished by comparison of retention time and fragmentation pattern with mass spectra in the NIST spectral library stored in the computer software (version 1.10 beta, Shimadzu) of the GC-MS along with the possible pharmaceutical roles of each bio molecule as per Dr. Duke's Phytochemical and ethnobotanical data base (National Agriculture Library, USA) and others as shown in Table 1[30].

Some work has been reported on the medicinal role of Shaddharana churnam. Gujarathi *et al*, 2015 have done a critical review of Shaddharana churna[31]. Dwivedi and Pande, 2017 have worked on the clinical effect of this medicine on malabsorption syndrome [32]. Mane *et al,* 2019 have reported the role of this medicine on Amlapitta (acidity).[33] In the present study, Table 1 indicate the presence of some molecules such as Cyclobutane-1,1-dicarboxamide, N,N'-di-benzoyloxy-, Hexadecanoic acid, methyl ester, n-Hexadecanoic acid, 12,15-Octadecadienoic acid, methyl ester, 9,12-Octadecadienoic acid (Z,Z)-, 15-Hydroxypentadecanoic acid, Decanedioic acid, bis(2-ethylhexyl) ester, .gamma.-Sitosterol etc. which have medicinal role that could help in the cure of ailments which are treated by Shaddharana churnam.

CONCLUSION

The various molecules present in Saddharana churnam do possess some medicinal roles which augur well with its medicinal role. There are some molecules whose medicinal roles are not known and it will be of interest to work on these molecules.

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Table1. Indicates the retentions time, types of possible compound, their molecular formulae, molecular mass, peak area and their medicinal roles of each compound as shown in the GC MS profile of Shaddharana Churnam

Sl. No	Retention Time	Compound Name	Mol. Formula	Mol. Weight	% Peak Area	Possible medical Role
1	5.63	Cyclobutane-1,1-dicarboxamide, N,N'-di-benzoyloxy-	C20H18N2O6	382.1	4.48	Anaphylactic, Antitumor, Arylamine-N-Acetyltransferase-Inhibitor. Decreases Norepinephrine Production, Down regulation of nuclear and cytosol androgen reuptake, GABA-nergic, Increases Natural Killer (NK) Cell Activity, Inhibits Production of Tumor Necrosis FactorAntitumor, anticancer, myoneuro-stimulant, decreases norepinephrine production, NADH-Oxidase inhibitor, NADH-Ubiquinone Oxidoreductase inhibitor
2	5.76	Methanol, oxo-, benzoate	C8H6O3	150	1.11	Not known
3	9.36	Ethanone, 1-(3-hydroxy-4-methoxyphenyl)-	C9H10O3	166.1	3.54	Not known
4	14.20	Hexadecanoic acid, methyl ester	C17H34O2	270.3	3.84	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity

5	14.57	n-Hexadecanoic acid	C16H32O2	256.2	3.57	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
6	15.73	12,15-Octadecadienoic acid, methyl ester	C19H34O2	294.3	10.10	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
7	15.79	9,12,15-Octadecatrienoic acid, methyl ester, (Z,Z,Z)-	C19H32O2	292.2	12.45	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
8	16.06	Methyl stearate	C19H38O2	298.3	3.09	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor
9	16.12	9,12-Octadecadienoic acid (Z,Z)-	C18H32O2	280.2	5.04	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
10	16.18	9-Octadecenoic acid, (E)-	C18H34O2	282.3	19.27	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor, Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
11	17.47	1,15-Pentadecanedioic acid	C15H28O4	272.2	1.41	Catechol-O-methyl-Transferase Inhibitor, methyl Donar, Methyl Guanidine Inhibitor,

						Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
12	18.52	Butyl 6,9,12-hexadecatrienoate	C20H34O2	306.3	1.22	Not known
13	18.83	Butyl 9,12-octadecadienoate	C22H40O2	336.3	9.20	Not known
14	19.09	15-Hydroxypentadecanoic acid	C15H30O3	258.2	3.05	Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
15	19.41	Bis(2-ethylhexyl) phthalate	C24H38O4	390.3	4.43	Not known
16	21.33	Decanedioic acid, bis(2-ethylhexyl) ester	C26H50O4	426.4	2.48	Acidifier, Arachidonic acid inhibitor, Increases Aromatic Amino acid Decarboxylase activity
17	22.01	Pentacosane	C25H52	352.4	1.55	Not known
18	23.39	Desmosterol	C27H44O	384.3	1.39	Not known
19	24.38	.gamma.-Sitosterol	C29H50O	414.4	3.33	PPAR-gamma antagonist
20	24.77	Betulin	C30H50O2	442.4	4.37	Not known
21	25.40	Lup-20(29)-en-3-ol, acetate, (3.beta.)-	C32H52O2	468.4	1.09	Not known

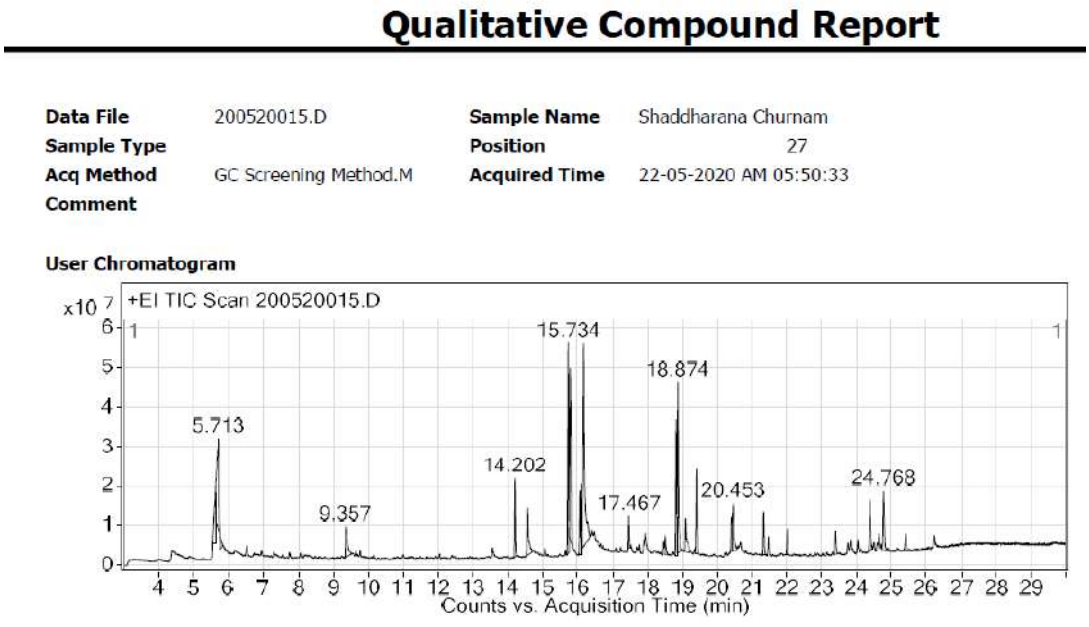

Figure 1. Depicts the GC MS profile of Shaddharanachurnam

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RESEARCH ARTICLE

Nanoparticulate Drug Delivery Systems for Improving the Bioavailability of Drugs

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ABSTRACT

In the recent years, the use of polymeric nanoparticles as carriers for a wide range of drugs for therapeutic applications has been increased due to their versatility and wide range of properties. Nanoparticles provide the action at the desired sites and thus gaining importance nowadays. With these nanoparticles the specific targeting to various cells or which are responsible for cellular internalization and cellular uptake.

Keywords: Nanoparticles, polymers, coacervation, zetapotential, active pharmaceutical ingredients.

INTRODUCTION

Colloidal drug delivery system provides number of advantages over conventional dosage forms. Due to their small size colloidal preparations lend themselves to parenteral preparations and may be useful as sustained-release injection for the delivery to specific organ or target site. Nanotechnology has potential for numerous applications in different food industries. Nanoencapsulation of bioactive components involved forming nm carriers with diameter ranging from 1 to 1000 nm. Such system can be partially useful for control release application in pharmaceutics cosmetics and food industry. Nanopurticulate drug delivery system have beneficial advantages such as increased surface area and enhanced bioavailability of compounds along with limited toxicity. There are variety of submicron particles polymer based nanoparticles are unique compared to other nanoparticle system due to their better encapsulation, control release and less toxic properties. Nanoparticulate drug delivery system is usually intended for

oral, parenteral or topical route with the ultimate objective being the alteration of pharmacokinetic profile of active molecule. Nanotechnology is a science of the small the prefix nano comes from ancient Greek word means "dwarf". Nanotechnology provides opportunity for the development of material including those for medical application, where conventional techniques reach their limits. Nanotechnology represents the design production and application of material at atomic, molecular and macromolecular scale in order to produce new nanosized material. The name nanoparticle is combined name for both nanosphere and nanocapsules. Nanospheres are matrix system in which drug is uniformly dispersed while nanocapsules other system in which drug is surrounded by a unique polymeric membrane. The major goal in designing nanoparticles as a delivery system for control particle size, surface properties and release of pharmacologically active agent so as to achieve site specific action of the drug at rational rate and dose. [1], [2], [4], [11].

Many nanoparticles have a large surface area which enables them to be an integral part of effective drug delivery system. In recent years biodegradable polymeric nanoparticles, particularly those with hydrophobic polymer such as poly ethylene glycol known as long circulating particles have been used as a potential drug delivery devices because of their ability to circulate for a prolonged period of time to target particular organ as a career of DNA in gene therapy and their ability to deliver proteins peptides and genes [3].

Advantage of nanotechnology is to provide the safe and the effective medicine to influence of both pharmaceutical and biotechnological industry. Application in various fields of life sciences such as separation technologies, histological studies, clinical diagnosis and as a drug delivery systems. The first industrial production of nanomaterial occurs in the early 20th century with the production of carbon black and later in 1940 fused silica. The use of nanotechnology for treatment, identification, monitoring and managing biological system have been recently referred to as nanomedicine [5], [6], [7], [8].

TYPES OF NANOPARTICLES

Depending upon the material used for preparing nanoparticles, they are classified into following three groups

A. Polymer based nanoparticles

B. Lipid based nanoparticles

C. Lipid-polymer hybrid nanoparticles.

Polymer based nanoparticles

Polymer nanoparticles are nano-sized colloidal particles in which a therapeutic agent can be loaded within their polymeric matrix or absorbed or conjugated onto the surface. The nanoparticles have been shown to improve bioavailability and enhance drug solubility because of reduced particle size upto nano size and encapsulating the drug into the water-soluble polymer. This nanoparticles serve as an excellent vehicle for delivery of a number of biomolecules, drugs, genes and vaccines. Nanoparticles were mainly formulated from poly alkyl cyanoacrylate. They easily cross mucosal barrier due to their size but they have short lifespan due to Rapid clearance from the body of phagocytic cells. Surface modification protect nanoparticle from being phagocytosed and removal from the vascular system after intravenous injection. The use of polymeric nanoparticles for delivery strategy that to optimise therapeutic effect while minimising adverse effect. Nanoparticles can be prepared from a variety of materials. Selection of the base polymer is based on many factors such as

- Size of desired nanoparticles.
- Properties of the drug to be encapsulated in polymer.
- Surface characteristics and functionality.
- Degree of biodegradability, biocompatibility and toxicity.
- Drug release profile.
- Antigenicity of final product.

Examples for naturally occurring biodegradable polymers used for preparing nanoparticles are cellulose, gelatin, chitosan and alginate. Examples for synthetic biodegradable polymer used to prepare nanoparticles include poly lactic acid, poly-lactide coglycolide (PLGA), polyunhydrides, Poli-caprolactone, poly alkyl cyanoacrylate and polyphosphazene.

Lipid based nanoparticles.

Due to the toxicity of polymers, presence of solvent residue in compound during production and purification cost, degradability, lack of suitable large scale production unit, requirement of high purity and quality of biodegradable polymers, polymer nanoparticles are limited in use. Lipid based nanoparticles is composed of lipids with a lipid core. Lipid nanoparticles can be synthesized by combining an oil phace with phospholipids as emulsifiers. They can be synthesized by methods such as high pressure homogenization. Most important lipid based nanoparticles are solid lipid nanoparticles, nanostructured lipid carriers and lipids drug conjugate. Lipid nanoparticles are used commonly because of its characteristics like suitable for drug delivery, use of physiological tolerated lipid, large scale production, protection of drug from degradation, improved bioavailability, minimum level of toxicity and controlled release characteristics. Due to low cytotoxicity of lipid nanoparticles these are used for application of DNA or RNA.

Lipid polymer hybrid nanoparticles

Lipid-polymer hybrid nanoparticles combines the merits of both lipid based nanoparticles and polymer based nanoparticles. Lipid polymer hybrid nanoparticles has a robust drug delivery platform with high drug encapsulation, tunable and sustained drug release profile with excellent serum stability and differential targeting of cells or tissues.

Lipid polymer hybrid nanoparticles comprised of three distinct functional components.

a) A hydrophobic polymer which is used to encapsulate poorly water soluble drugs.

b) A hydrophilic polymer shell which enhance lipid polymer hybrid nanoparticles stability and increase half life during systemic circulation.

c) A lipid shell at the interface of the core and the shell act as a molecular wall to promote retention of drug inside polymeric core, so as to enhance drug encapsulation efficiency, increasing drug loading and controlling drug release. Polymeric core and shell are associated to hydrophobic interactions, Van der walls forces, electrostatic interactions or non covalent forces. This lipid polymer hybrid nanoparticles have been demonstrated to include unique advantages of both lipid-based and polymer based nanoparticles by holding great promise as a delivery vehicles for various medical applications [9].

PREPARATION OF NANOPARTICLES

In the preparation of nanoparticles different types of matrix materials are used. The selection of method for preparation of nanoparticles based on the following characteristics.

- Nanoparticle size
- Permeability and surface charge of nanoparticles.
- Level of biodegradability and biocompatibility must be optimum.
- Material must be non toxic.
- Solubility profile and stability of drug should not be affected.
- Should show drug release profile.
- Must be immunogenic.

Nanoparticles have been prepared most frequently by

Dispersion of preformed polymers

Dispersion of preformed polymers is a common technique used to prepare biodegradable nanoparticles from poly lactic acid (PLA), poly D,L glycolide (PLG), poly D,L- lactide co- glycolide (PLGA), and Poly cyanoacrylate (PCA). This technique can be used in various ways as described below.

Solvent evaporation method

In this method the polymer is dissolved in an organic solvent such as dichloromethane, chloroform or ethyl acetate which is also used as a solvent for dissolving the hydrophobic drug. The mixture of polymer and drug solution is then emulsified in an aqueous solution containing a surfactant or emulsifying agent to form an oil-in-water emulsion. After the formation of stable emulsion the organic solvent is evaporated either by reducing the pressure or by continuous stirring. Method was found to be influenced by the type and concentration of stabilizer, homogenizer speed and polymer concentration. In order to produce small particle size often a high speed homogenization or ultrasonication may be used.

Spontaneous emulsification or solvent diffusion method

This is a modified version of solvent evaporation method, in this method the water miscible solvent with a small amount of water immiscible organic solvent is used as an oil phase. Due to spontaneous diffusion of solvents and interfacial turbulence is created between the two phases leading to formation of small particles. The concentration of water miscible solvent increases, a decrease in size of the particle can be achieved. Both solvent evaporation and solvent diffusion method can be used for hydrophobic or hydrophilic drugs. In the case of hydrophilic drug a multiple emulsion w/o/w need to be formed with the drug dissolved in the internal aqueous phase.

Polymerization method

In this method monomers are polymerized to form nanoparticles in an aqueous solution. Drug is incorporated either by being dissolved in the polymerization medium or by adsorption onto the nanoparticles after polymerization completed. The nanoparticle suspension is then purified to remove various stabilizers and surfactant employed for polymerization by ultracentrifugation for resuspending the particle in an isotonic surfactant free medium. This technique has been reported for making poly butyl cyanoacrylate or poly alkyl cyanoacrylate nanoparticles depending on the concentration of surfactant and stabilizers used.

Coacervation or ionic gelation method

Many research has been focused on the preparation of nanoparticles using biodegradable hydrophilic polymers such as chitosan, gelatin and sodium alginate. The method for preparing hydrophilic chitosan nanoparticles by ionic gelation method involves a mixture of two aqueous phases of which one is the polymer chitosan and the other is a poly anion sodium tripolyphosphate. In this method positively charged amino group of chitosan interacts with negative charged tripolyphosphate to form coacervates with size in the range of nanometers. Coacervates are formed as a result of electrostatic interaction between two aqueous phase where is ionic gelation involves the material undergoing transition from liquid to gel due to ionic interaction condition at room temperature.

Supercritical fluid technology

Conventional methods such as solvent extraction, evaporation, solvent diffusion and organic phase separation method require the use of organic solvents which are hazardous to the environment as well as to physiological system. Therefore the supercritical fluid technology has been investigated as an alternative to prepare biodegradable micro and nanoparticles because supercritical fluids are environmentally safe. A supercritical fluid can be generally defined as a solvent at a temperature about its critical temperature, at which the fluid remains a single-phase regardless of pressure. Supercritical carbon dioxide is the most widely used supercritical fluid because of its mild critical condition, non toxicity, non-inflammability and low price. The most common processing techniques involved supercritical fluids are supercritical antisolvent (SAS) and Rapid expansion of critical solution (RESS). The process SAS employs a liquid solvent example methanol which is completely miscible with supercritical fluid to dissolve the solute to be micronized at process conditions because the solute is insoluble in supercritical fluid the extract of the liquid solvent by supercritical fluid leads to the instantaneous precipitation of the solute resulting the formation of nanoparticles.

RESS differs from the SAS process in that its solute is dissolved in a supercritical fluid and then the solution is rapidly expanded through a small nozzle into a region lower pressure. Thus the solvent power of supercritical fluid dramatically decrease and the solute eventually precipitates. This technique is clean because the precipitate is basically solvent-free. RESS and its modified process have been used for the product of polymeric nanoparticles. Supercritical fluid technology is environment friendly and suitable for mass production and specially designed equipments are more expensive [6], [7], [10].

CHARACTERIZATION OF NANOPARTICLE

Nanoparticles are generally characterized by their surface morphology by using advanced microscopic techniques such as scanning electron microscopy (SEM), transmission electron microscopy (TEM) and atomic force microscopy. Average particle diameter, distribution and charge affect the physical stability and *in vivo* distribution of nanoparticles. Electron microscopy techniques are very useful in ascertaining the shape of polymeric nanoparticles, which may determine their toxicity, effect of physical stability and redispersibility of the polymer dispersion as well as their in vivo performance.

Particle size

Particle size distribution and morphology are the most important parameters of characterization of nanoparticles. Morphology and size are measured by electron microscopy. The major application of nanoparticles is in drug release and drug targeting. It has been found that particle size affect the drug release, smaller particle offer large surface area as a result most of the drug loaded and will be exposed to the particle surface leading to fast drugs release. The main drawback is that, smaller particles tend to aggregate during storage and transportation of nanoparticle dispersion, hence there is a compromise between a small size and maximum stability of nanoparticles. Degradation can also be affected by the particle size, for instance the degradation rate of poly (lactic-co- glycolic acid) was found to increase with increasing particle size. The different tools used for determining nanoparticle size are discussed below

Dynamic light scattering (DLS)

Currently the fastest and most popular method of determining particle size is photon correlation Spectroscopy (PCS) or dynamic light scattering (DLS). Dynamic light scattering is widely used to determine the size of Brownian nanoparticles in colloidal suspension in the nano and submicron range. Striking monochromatic light on to a solution of spherical particle in Brownian motion causes a doppler shift, when the light hit the moving particles and changing the wavelength of the incoming light this change is related to the size of the particle. It is impossible to extract the size distribution and give a description of the particles motion in the medium in measuring the diffusion coefficient of the particle and using the autocorrelation function. The photon correlation spectroscopy is the most frequently used technique for accurate estimation of particle size and size distribution based on DLS.

Scanning electron microscopy (SEM)

Scanning electron microscopy is giving morphological examination with direct visualisation. Technique based on electron microscopy offer several advantages and moreover they provide limited information about the size distribution and true population average. For scanning electron microscopic characterization of nanoparticle solution should be first converted into dry powder which is then mounted on a sample holder by coating with a conductive metal such as gold. The sample is then scanned with a focused fine beam of electrons. The surface characteristics of the sample are obtained from secondary electrons emitted from the sample surface. The nanoparticle must be able to withstand scanning and the electron beam can damage the polymer. The mean size obtained by scanning electron microscope is comparable with the result obtained by dynamic light scattering. Moreover these techniques are time-consuming, costly and frequently need complementary information about sizing distribution.

Transmission electron microscopy

Transmission electron microscopy operates on different principle than scanning electron microscope, yet it often brings same type of data. The sample preparation for transmission electron microscope is complex and time-consuming because of its requirement to be ultra thin for the electron transmittence. The nanoparticles dispersion is deposited onto support grids or films. To make nanoparticles, withstand the instrument vacuum and facilitate handling, they are fixed using either negative staining material such as phosphotungstic acid or derivatives uranyl acetate etc or by plastic embedding. Alternate method is to expose the sample to liquid nitrogen temperatures are embedding in vitreous ice. The surface characteristics of the sample obtained when a beam of electron is transmitted through the ultra thin sample interacting with the sample as it passes through.

Atomic force microscopy

Atomic force microscopy of ultra-high resolution in particle size measurement and is based on a physical scanning of samples at submicron level using a prob tip of atomic scale. The instrument provides a topographical map of sample based on forces between the tip and the sample surface. Samples are usually scanned in contact or non contact more depending on their properties. In contact mode the topographical map is generated by tapping the prob onto the surface across the sample and prob moves over the conducting surface in non-contact mode. The main advantage of atomic force microscopy is its ability to image non conducting samples without any specific treatment, thus allowing imaging of delicate biological and polymeric nano and microstructures. Atomic force microscopy provides the most accurate description of size and size distribution and requires no mathematical treatment. Moreover particle size obtained by atomic force microscopy technique provides real picture with help understand the effect of various biological conditions.

Surface charge

The nature and intensity of the surface charge of nanoparticle is very important as it determines their interaction with the biological environment as well as their electrostatic interaction with bioactive compounds. Stability is analysed through zeta potential of nanoparticles this potential is an indirect measure of surface charge. It corresponds to potential difference between the outer plane and the surface of the shear. The measurement of the zeta potential allows for predictions about the storage stability of colloidal dispersion. High Zeta potential value whether positive or negative should be achieved in order to ensure stability and avoid aggregation of particle. The extent of surface hydrophobicity can then be predicted from the value of Zeta potential. The Zeta potential can also provide information regarding the nature of material encapsulated within the nanoparticles coated onto the surface.

Surface hydrophobicity

Surface hydrophobicity can be determined by several techniques such as hydrophobic interaction chromatography, biphasic partitioning, adsorption probes, contact angle measurement etc. Recently several sophisticated analytical techniques are introduced for surface analysis of nanoparticles. X-Ray Photon correlation spectroscopy permit the identification of specific chemical groups on the surface of nanoparticle.

Drug loading

Nanoparticle should have a high drug loading capacity thereby reduce the quantity of matrix material for administration. Drug loading can be done by two methods

Incorporating at the time of nanoparticle production (incorporation method)

Absorbing the drug after formation of nanoparticle by incubating the carrier with concentrated drug solution. (adsorption or absorption technique)

Drug loading and Entrapment efficiency very much depend on the solid state drug solubility in matrix material or polymer which is related to the polymer composition, the molecular weight, that drug polymer interaction and the presence of end functional group.

Drug release

The main aim of nanotechnology is to deliver drugs, hence understanding the manner and extent to which the drug molecules are released is important. In order to obtain such information most release methods require that the drug and its delivery vehicle be separated. The drug loading of nanoparticle is generally defined as the amount of drug bound per polymer, it could also be given a percentage relative to the polymer. The technique used to find this analysis is classical analytical methods like UV Spectroscopy or high performance liquid chromatography (HPLC), ultracentrifugation, ultrafiltration, gel filtration or Centrifugal ultrafiltration. Quantification is performed with the UV Spectroscopy or HPLC. Drug release assay are also similar to drug loading assay which is assessed for a period of time to analyse the mechanism of drug release [3], [4], [11].

CONCLUSION

Nanoparticles are a contribution to the drug delivery development for formulation by various methods, mainly the interfacial polymerization and interfacial nano-deposition. Nanoparticles can be released as the monodisperse particles with well-defined biochemical, electrical, optical, as well as magnetic properties. In drug delivery system, they are confined to suit the complexity of the application as they intend to produce contents in response to a specific bimolecular triggering action mechanism. Nanoparticles have various applications in various fields of the agrochemicals, waste water treatments, genetic engineering, cosmetics, cleaning products, as well as in adhesive component. They are also used in encapsulation of enzymes, adhesives, catalysts, polymers, oils, inorganic micro and nanoparticles, latex particles, and even the biological cells. In conclusion, they can be used in the delivery of active pharmaceutical ingredients. Nanoparticles are the novel effective drug delivery systems in the up-coming future.

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REVIEW ARTICLE

A Complete Review on Herbal Excipients

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ABSTRACT

Excipients are fundamentally utilized as diluents, folios, disintegrants, cements, glidants and sugars in regular measurements structures like tablets and capsules. As the foundation of poisonousness and endorsement from administrative specialists represents an issue with engineered excipients. Regular polysaccharides are widely utilized for the advancement of strong dose structures. These polymers of monosaccharides (sugars) are cheap and accessible in an assortment of constructions with an assortment of properties.Whereas it also involves the presence and uses of natural ,synthetic reins such as gaur, karaya, xanthan gums ,pectins, menthol .,etc

Keywords: Gum, herbal excipients, polymers, polysaccharides

INTRODUCTION

Excipients are fundamentally utilized as diluents, folios, disintegrants, cements, glidants and sugars in regular measurements structures like tablets and capsules. As the foundation of poisonousness and endorsement from administrative specialists represents an issue with engineered excipients, of late more interest is being shown by analysts in natural excipients [1]. The downside presented by weighty metal defilement regularly connected with home grown excipients is supplanted by their absence of harmfulness, simple accessibility, and monetary contemplations in drug industry when contrasted with their engineered partners. Present day purchasers search for normal fixings in food, medications, and beauty care products as they accept that anything regular will be more protected and without incidental effects [2].

The conventional view that excipients are idle and don't apply any helpful or natural activity or adjust the organic activity of the medication substance has changed and it is presently perceived that excipients might conceivably impact the rate or potentially degree of ingestion of a medication [3]. As natural excipients are non poisonous and viable, they play a significant part to play in drug plan. Thus, this paper is an endeavor to audit natural excipients utilized in NDDS.

POLYSACCHARIDES IN PHARMACEUTICALS

Regular polysaccharides are widely utilized for the advancement of strong dose structures [4]. These polymers of monosaccharides (sugars) are cheap and accessible in an assortment of constructions with an assortment of properties. They are profoundly steady, protected, non-harmful, and hydrophilic and gel shaping in nature. Gelatins, starch, guar gum, amylase and karaya gum are a couple polysaccharides ordinarily utilized in measurements structures[5]. Non-starch, straight polysaccharides stay flawless in the physiological climate of the stomach and the small digestive tract, however are corrupted by the bacterial occupants of the human colon which make them possibly valuable in designated conveyance frameworks to the colon. Natural polysaccharides are broadly utilized for the advancement of strong measurement structures. These polymers of monosaccharides (sugars) are modest and accessible in an assortment of designs with an assortment of properties[6]. They are exceptionally steady, protected, non-poisonous, and hydrophilic and gel shaping in nature. Gelatins, starch, guar gum, amylase and karaya gum are a couple polysaccharides normally utilized in measurement structures. Non-starch, straight polysaccharides stay unblemished in the physiological climate of the stomach and the small digestive tract, however are corrupted by the bacterial occupants of the human colon which make them possibly helpful in designated conveyance frameworks to the colon.

PECTINS

Pectins are non-starch, direct polysaccharides removed from the plant cell dividers. They are overwhelmingly direct polymers of mostly (1-4)- connected D-galacturonic corrosive deposits hindered by 1,2-connected L-rhamnose buildups with a couple hundred to around 1,000 structure blocks for each particle, comparing to a normal sub-atomic load of around 50 000 to around 1 80 000. Being dissolvable in water, gelatin can't protect its medication load viably during its section through the stomach and small digestive tract [7]. It was tracked down that a layer of significant thickness was required to ensure the medication center in recreated in vivo conditions. Consequently the center was moved to the advancement of less solvent subordinates of gelatin which get corrupted by the colonic microflora. Calcium salts of gelatin diminished their dissolvability by framing an egg-box design [8]. To conquer the downside of high dissolvability of gelatin, blended movies of gelatin in with ethyl cellulose were explored as a covering material for colon-explicit medication conveyance. These movies consolidated the colon explicit corruption properties of gelatin with the defensive properties of the water insoluble polymer ethyl cellulose.

Polymeric hydrogels are generally utilized as controlled-discharge lattice tablets. Sungthongjeen et al. explored the high-methoxy gelatin for its expected worth in controlled-discharge grid details. The impacts of pressure power, proportion of medication to gelatin, and sort of gelatin on drug discharge from framework tablets were likewise explored[9]. The aftereffects of the in vitro discharge studies showed that the medication discharge from packed framework tablets arranged from gelatin can be altered by changing the sum and the kind of gelatin in the grid tablets. An exceptionally low dissolvability gelatin subordinate (pectinic corrosive, level of methoxylation 4%) was observed to be appropriate as an excipient for pelletisation by expulsion/spheronisation. The limit as an expulsion help was observed to be high; even definitions containing just 20% pectinic corrosive brought about almost round pellets. All pectinic corrosive pellets were precisely steady, had a viewpoint proportion of around 1.15-1.20 and delivered 30-60% of a low solvency model medication inside 15 min both in recreated gastric liquid (0.IM HCl) and digestive liquid (phosphate cradle pH 6.8).

Miniature particulate polymeric conveyance frameworks have been proposed as a potential way to deal with further develop the low bioavailability qualities shown by standard ophthalmic vehicles (collyria). In this setting gelatin

microspheres of piroxicam were ready by the shower drying procedure. In vivo tests in hares with scatterings of piroxicam-stacked microspheres additionally demonstrated a huge improvement of piroxicam bioavailability in the watery humor (2.5-crease) when contrasted and business piroxicam eyedrops.

Musabayane et al. researched the reasonableness of amidated gelatin as a lattice fix for transdermal chloroquine conveyance with an end goal to veil the unpleasant taste when orally managed. The outcomes recommend that the gelatin chloroquine fix network arrangement has likely applications for the transdermal conveyance of chloroquine and maybe in the administration of intestinal sickness. Calcium pectinate nanoparticles to convey insulin were ready as a potential colonic conveyance framework by ionotropic gelation[10]. According to the food business, folic corrosive fused microcapsules were arranged utilizing alginate and blends of alginate and gelatin polymers to further develop soundness of folic corrosive. Folic corrosive strength was assessed with reference to epitome effectiveness, gelling and solidifying of cases, capsular maintenance during drying and capacity. The mixed alginate and gelatin polymer framework expanded the folic corrosive embodiment effectiveness and diminished spillage from the containers when contrasted with those made with alginate alone, they showed higher folic corrosive maintenance after freeze drying and capacity.

Corresponding to beauty care products, utilizing citronella! as a model compound, gelatin gel details were assessed for controlled aroma discharge by dynamic and static techniques[11]. These plans showed a drawn out term of aroma delivery and restriction of scent adsorption to the receptor skin layers. The expansion in gelatin focuses smothered the aroma discharge by a dissemination system, in this way demonstrating that gelatin/calcium microparticles are promising materials for controlled scent discharge.

ALGINATES

Alginates are regular polysaccharide polymers segregated from the earthy colored ocean weed (Phaeophyceae)[12]. Alginic corrosive can be changed over into its salts, of which sodium alginate is the significant structure as of now utilized. A direct polymer comprising of D- mannuronic corrosive and L-guluronic corrosive deposits orchestrated in blocks in the polymer chain, these homogeneous squares (made out of either corrosive buildup alone) are isolated by blocks made of irregular or exchanging units of mannuronic and guluronic acids. Alginates offer different applications in drug conveyance, for example, in network type alginate gel dabs, in liposomes, in balancing gastrointestinal travel time, for nearby applications and to convey the bio atoms in tissue designing applications.

Bioadhesive sodium alginate microspheres of metoprolol tartrate for intranasal fundamental conveyance were ready to stay away from the main pass impact, as an elective treatment to infusion, and to acquire worked on remedial adequacy in the treatment of hypertension and angina pectoris. The microspheres were arranged utilizing emulsification-cross connecting strategy [13]. In vivo concentrates on demonstrated altogether worked on helpful viability of metoprolol from microspheres, with supported and controlled hindrance of isoprenaline-initiated tachycardia as contrasted and oral and nasal organization of medication arrangement. Another addition, fundamentally comprising of alginates with various hydroxyethylcellulose content was created to keep a steady medication level over a specific period in the eye, which can't be accomplished by ordinary eye drop application[14]. This review showed great resilience of the new calcium-alginate-embed applied to the visual surface for controlled medication releaseu.. To accomplish 24 h discharge profile of water dissolvable medications, sodium alginate definition grids containing thickener or zinc acetic acid derivation or both were examined.

The arrival of the medication from the sodium alginate plan containing just thickener was finished inside 12 h in the recreated gastrointestinal liquid, while the medication discharge from the sodium alginate detailing containing just zinc acetic acid derivation was finished inside 2 h in a similar medium. Just the sodium alginate definition, containing both thickener and zinc acetic acid derivation accomplished a 24 h discharge profile, either in the mimicked gastrointestinal liquid or in the pH change medium (pH 1.2). The helical design and high thickness of thickener potentially forestall zinc particles from diffusing out of the ranitidine HCL sodium alginate-thickener zinc

acetic acid derivation lattice so that zinc particles respond with sodium alginate to shape zinc alginate hasten with a cross-connecting structure. The cross-connecting design may control a profoundly water-dissolvable medication discharge for 24 h [15].

In a relative report, alginate detailing seemed, by all accounts, to be better compared to the polylactide-co-glycolide (PLG) definition in working on the bioavailability of two clinically significant antifu ngal medications clotrimazole and econazole. The nanoparticles were ready by the emulsion-dissolvable dissipation strategy in the event of PLG and by the cation-initiated controlled gelification if there should arise an occurrence of alginate11.

STARCHES

It is the chief type of starch hold in green plants and particularly present in seeds and underground organs [16]. Starch happens as granules (starch grains), the shape and size of which are normal for the species, as is additionally the proportion of the substance of the main constituents, amylase and amylopectin. Various starches are perceived for drug use. These incorporate maize (Zea mays), rice (Oryza sativa), wheat (*Triticum aestivum*), and potato *(Solanum tuberosum*).

Changed starch was tried for general pertinence of a new pregelatinized starch item in straightforwardly compressible controlled-discharge lattice frameworks. It was ready by enzymatic debasement of potato starch followed by prec1p1tation (retrogradation), filtration and washing with ethanol. The benefits of the material incorporate simplicity of tablet readiness, the capability of a steady delivery rate (zero-request) for a drawn out timeframe and its capacity to fuse high rates of medications with various physicochemical properties. Delivery rates from retrograded pregelatinized starch tablets can be upgraded or diminished to the ideal profile by various boundaries like calculations of the tablet, compaction power and the fuse of extra excipients.

To convey proteins or peptidic tranquilizes orally, microcapsules containing a protein and a proteinase inhibitor were ready[17]. Starch/ox-like serum egg whites blended walled microcapsules were arranged utilizing interfacial cross-connecting with terephthaloyl chloride. The microcapsules were stacked with local or amino-secured aprotinin by joining protease inhibitors in the fluid stage during the cross-connecting measure. The defensive impact of microcapsules with aprotinin for ox-like serum egg whites was uncovered in vitro[18].

Acetylating of starch extensively diminishes its enlarging and enzymatic corruption. Subsequently, starch-acetic acid derivation (SA) based conveyance frameworks were tried for controlled medication conveyance. It was demonstrated that acetylation of potato starch can considerably impede drug discharge by planning and assessing movies of local starch and acetylated starch. Ox-like serum egg whites (BSA, mol. wt. 68 000), FITC- dextran (mol. wt. 4400), timolol (mol. wt. 332, log P=l.91) and sotalol-HCl (mol. wt. 308, log P=-0.62) were utilized as model medications. Every one of the model medications were delivered quickly from the potato starch film in PBS pH 7.4 with and without alpha-amylase in the disintegration medium (t50% differed from 0.17 to 3.37 h). When contrasted with the potato starch film, every one of the concentrated on drugs were delivered at a significantly more slow rate from the SA films in the relating media. A similar report was completed to assess drug discharge from the SA microparticles (SA mps) and SA films.

The normal level of acetyl replacement (DS) per glucose buildup in the starch was either 1.9 (SA DS 1.9) or 2.6 (SA DS 2.6). Timolol, calcein and BSA were utilized as model medications. This review showed the accomplishment of slow arrival of various sub-atomic weight model medications from the SA mps and movies when contrasted with quick delivery from the local starch arrangements.

GUMS

Gums are clear and undefined substances created by the plants. Generally obsessive items, gums are delivered when the plant is developing under troublesome conditions or when harmed[19]. Gums are plant

hydrocolloids and might be anionic or non ionic polysaccharides. On hydrolysis gums yield sugar and salts of uronic corrosive. Gums are clear and undefined substances created by the plants. Generally obsessive items, gums are delivered when the plant is developing under troublesome conditions or when harmed. Gums are plant hydrocolloids and might be anionic or non ionic polysaccharides. On hydrolysis gums yield sugar and salts of uronic corrosive[20].

GUAR GUM

Guar gum got from the seeds of *Cyamopsis tetragonolobus* (Family Leguminosae) is a normally happening galactomannan polysaccharide[21]. It is comprised of a straight chain of - D-mannopyranose joined by - (1-4) linkage with a-D- galactopyranosyl units connected by 1, 6-joins in the proportion of 1:22. Guar gum is utilized in colon-conveyance frameworks because of its medication discharge hindering property and helplessness to microbial corruption in the internal organ. Center tablets containing 5-aminosalisylic corrosive (5-ASA) were ready by wet granulation with starch glue and were pressure covered with covering definitions containing various amounts of guar gum The review affirmed that specific conveyance of 5-ASA to the colon can be accomplished utilizing guar gum as a transporter as a pressure covering over the medication center.

Further, guar gum-based grid tablets of rofecoxib were ready for their planned use in the chemoprevention of colorectal malignant growth. In vivo studies showed postponed Tmax, delayed retention time and diminished Cmax demonstrating that rofecoxib was not delivered altogether in stomach and small digestive tract, however was conveyed to colon bringing about a sluggish assimilation of the medication and making it accessible for nearby activity in human colon.

While trying to plan oral controlled medication conveyance frameworks for exceptionally water- dissolvable medications utilizing guar gum as a transporter as three-layer network tablets, trimetazidine dihydrochloride was picked as a model medication on account of its high water solvency. Both grid tablets just as three layer framework tablets were ready and assessed[22]. The three-layer guar gum network tablet gave the necessary delivery rate comparable to the hypothetical delivery rate for guar gum details implied for twice every day organization.

The outcomes showed that guar gum, as three-layer framework tablets, is a possible transporter in the plan of oral controlled medication conveyance frameworks for exceptionally water-solvent medications, for example, trimetazidine dihydrochloride. A similar report was done by utilizing metoprolol tartrate a model medication with high dissolvability. The outcomes demonstrated that guar gum, as three-layer grid tablets, is a likely transporter in the plan of oral controlled medication conveyance frameworks for exceptionally water-dissolvable medications like metoprolol tartrate. Another water dissolvable medication, diltiazem HCl has given controlled delivery tantamount with advertised supported delivery diltiazem HCl tablets (D-SR tablets), which are ready as lattice tablets with guar gum utilizing the wet granulation method.

KARAYA GUM

Karaya gum is acquired from *Sterculia urens* (Family sterculiaceae) is a somewhat acetylated polymer of galactose, rhamnose, and glucuronic corrosive. Swellable hydrophilic normal gums like thickener and karaya gum were utilized as release- controlling specialists in delivering straightforwardly packed frameworks. Caffeine and diclofenac sodium, which are having various solubilities in watery medium were chosen as model medications [23]. Gum disintegration, hydration and medication discharge studies were completed utilizing a disintegration mechanical assembly (container strategy) at two tumult speeds. If there should arise an occurrence of thickener neither fomentation speed nor drug solvency had any critical impact on water take-up, yet lattices with the lower extent of gum created a lesser level of hydration. Interestingly, karaya gum showed a much lower hydration limit and a higher pace of disintegration, both particularly influenced by unsettling speed. Henceforth it was reasoned that medication discharge from xanthan and karaya gum frameworks relied upon unsettling velocity, dissolvability and extent of medication. Both xanthan and karaya gums created almost zero request drug discharge with the

disintegration component assuming a prevailing part, particularly in karaya gum lattices. Park et al. showed that mucoadhesive tablets arranged by karaya gum for buccal conveyance, had better glue properties as analyzed than guar gum and had the option to give zero-request drug discharge, however focuses more prominent than half w/w might be needed to give appropriate supported delivery.

XANTHAN GUM

Xanthan gum is a high sub-atomic weight extra cell polysaccharide created by the maturation of the gram-negative bacterium *Xanthomonas campestris*. The essential design of this normally delivered cellulose subordinate contains a cellulosic spine (- D-glucose buildups) and a trisaccharide side chain of - D- mannose- - D-glucuronicacid-a-D-mannose appended with substitute glucose deposits of the principle chain. The terminal D-mannose buildup might convey a pyruvate work, the circulation of which is subject to the bacterial strain and the aging conditions[24]. The non-terminal D-mannose unit in the side chain contains an acetyl work. The anionic person of this polymer is because of the presence of both glucuronicacid and pyruvic corrosive gatherings in the side chain. In one of the preliminaries, thickener showed a higher capacity to impede the medication discharge than engineered hydroxypropylmethylcellulose. Thickener and hydroxypropylmethylcellulose were utilized as hydrophilic matrixing specialists for getting ready changed delivery tablets of diltiazem HCL The measure of hydroxypropylmethylcellulose and thickener displayed critical impact on drug discharge from the tablets arranged by direct pressure strategy. It was inferred that by utilizing an appropriate mix of hydroxypropylmethylcellulose and thickener wanted altered medication delivery could be accomplished. Compaction and pressure properties of thickener pellets were assessed and drug discharge from tablets made of pellets was described[25]. Two kinds of pellets were ready by expulsion spheronisation. Details included thickener, at 16% (w/w) and diclofenac sodium or ibuprofen, at 10% (w/w) among other excipients [26]. Actual properties of pellets and tablets were investigated. Laser profilometry investigation and filtering electron microscopy of the upper surface and the outer layer of break of tablets uncovered that particles stayed as reasonable individual units after pressure measure. Pellets showed close compressibility degrees (49.9% for pellets involving diclofenac sodium and 48.5% for pellets containing ibuprofen). The arrival of the model medication from both kind of tablets uncovered various practices. Tablets made of pellets including ibuprofen delivered the model medication in a bimodal manner and the delivery conduct was portrayed as Case II vehicle instrument (discharge example of 0.93). Then again, the delivery conduct of diclofenac sodium from tablets made of pellets was atypical (discharge type of 0.70). For the last case, drug dispersion and disintegration were contending components of medication discharge.

By using maintenance properties of thickener and delivering properties of galactomannan, want discharge profile was accomplished in conveyance of theophylline[27]. Hydrophilic galactomannan is gotten from the seeds of the Brazilian tree Mimosa scabrella (Family Leguminosae). The grids made alone with thickener (X) showed higher medication maintenance for all fixations, contrasted and galactomannan (G) lattices that delivered the medication excessively quick. The grids arranged by blend of the two gums had the option to deliver close to zero-request drug discharge. The XG (cone 8%) tablets gave the necessary delivery rate (about 90% toward the finish of 8 h), with zero-request discharge energy.

TRAGACANTH

This gum is acquired from the parts of *Astragalus gummifer*, Family Leguminosae [28]. Tragacanth when utilized as the transporter in the detailing of 1-and 3-layer lattices delivered good delivery prolongation either alone or in mix with different polymers.

VOLATILE OILS

Volatile oils are by and large combinations of hydrocarbons and oxygenated compounds got from these hydrocarbons. Many oils are terpenoid in beginning; some of them are sweet-smelling subordinates blended in with terpenes (for example cinnamon and clove)[29]. A couple compounds (for example thymol and carvacrol) albeit sweet-smelling in structure, are terpenoid in beginning.

MENTHOL

Menthol is acquired by steam refining of the blooming highest points of *Mentha piperita* having a place with the family Labiatae[30]. A film directed transdermal helpful framework (TTS) of nimodipine utilizing 2%w/w hydroxypropylmethylcellulose (HPMC) gel as a repository framework containing menthol as infiltration enhancer and 60%v/v ethanol-water as dissolvable framework was ready. The in vivo assessment of nimodipine TTS fix was completed to discover the capacity of the created menthol-based TTS fix in giving the foreordained plasma grouping of the medication in human volunteers. The outcomes showed that the menthol-based TTS fix of nimodipine gave consistent plasma centralization of the medication with insignificant changes with further developed bioavailability in examination with the prompt delivery tablet dose structure.

Menthol was tried for working on the bioavailability of inadequately water-dissolvable ibuprofen in the rectum with poloxamer. The impacts of menthol and poloxamer 188 on the fluid dissolvability of ibuprofen were examined. The poloxamer gel with poloxamer 188 and menthol was observed to be a more compelling rectal dose structure for ibuprofen36. Terpenes, for example, menthol cineole and propylene glycol (PG) were tried as synthetic enhancers to further develop the skin entrance of propranolol [31]. Delivery and skin penetration energy of propranolol from film arrangements were analyzed in vitro concentrates on utilizing a Franz-type dissemination cell. In vitro skin pervasion studies showed that cineole was the most encouraging enhancer among the enhancers inspected.

CARAWAY

Caraway organic product comprises of the dried, ready products of Carum carvi (Umbelliferae). The unstable oil comprises of the ketone carvone and the terpene limonene [32]. In another endeavor, a limonene-based transdermal helpful framework (TTS) was ready to concentrate on its capacity to give the ideal consistent state plasma convergence of nicorandil in human volunteers. It was inferred that the limonene-based TTS of nicorandil gave the ideal plasma convergence of the medication for the foreordained timeframe with negligible changes and further developed bioavailability.

Along these lines a carvone based and nerodilol based transdermal restorative frameworks were arranged utilizing nicorandil as a model medication. It was reasoned that the two TTS of nicorandil gave the ideal in vivo controlled-discharge profile of the medication for the foreordained timeframe.

CONCLUSION

Today the pressure is on tolerant consistence and to accomplish this target there is a spray in the advancement of NDDS. As the natural excipients are promising biodegradable materials, these can be synthetically viable with the excipients in drug conveyance frameworks. Furthermore natural excipients are non-poisonous, uninhibitedly accessible, and more affordable contrasted with their engineered partners. They play a significant part to play in drug industry. Hence, in the years to come, there will be proceeded with interest in the regular excipients to have better materials for drug conveyance frameworks.

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RESEARCH ARTICLE

The Effect of Lambda in Recovering the Highly Corrupted Image using Adaptive Directional Lifting Induced Proximal Gradient Method

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ABSTRACT

Image completion have the many real time applications in machine learning, compressed sensing etc., The image with more than 80 percent lost information are solved using image completion algorithms. The applications are made the researchers to work and develop the Image completion algorithms. The transform-based optimization methods are able to recover the corrupted images more clearly. Here a new algorithm named Adaptive Directional Lifting Wavelet Transform (ADLWT) based regularizer has been introduced. It is able to recover the image at high corruption ratios. The ADLWT is predicts the corrupted values depending on the directions in such a way that perfectly matches. It is induced with the optimization method named Accelerated Proximal Gradient Line (APGL). The proposed algorithm is evaluated with the Full-Reference Image Quality Assessment (FRIQA) and No-Reference Image Quality Assessment (NRIQA) metrics. The results are improved with respect to image quality and structure information. The impact of lambda in the optimization and the optimal value is identified.

Keywords: Adaptive Directional Lifting, Optimization, ADL Regularizer, Directional Wavelets, Transform based optimization

INTRODUCTION

Wavelet transforms are playing a vital role in the Image and Video processing applications. The multi resolution, energy compaction and spacio–frequency localization are the factors lead to use in many real time applications. Most of the images have the energy in low frequency bands, so decomposition is very effective in image processing, computer vision and compressed sensing applications. The conventional lifting wavelet transform is performing the

filtering, in horizontal and vertical directions. The information present in the image can be identified with this operation, but that information is predicted based on horizontal and vertical operations. The diagonal information among the pixels is missing, it leads to loss of structural information in the reconstruction image. This drawback is can be overcome by Adaptive Directional Lifting Wavelet Transform [1-3]. It is able to predict the pixels values with diagonal operations as similar to horizontal/vertical operations in adaptive lifting.

The ADLWT determines the corrupted pixel value by utilizing the interpolated information between pixels. The interpolated information is 1/4 and 1/2 value of the neighboring pixels. Based on the angle, the comparison of neighborhood pixel value is considered [2]. At which position the difference is small that value will be considered and it will be replaced. The process requires several transformations in each pixel. Hence the computational consists is much higher than the traditional wavelet transform. If the image lost there details more the regular transform-based coding methods are alone not sufficient. The optimization approach is very essential in recovering the missing pixels in the corrupted image. The rank minimization algorithms are also proposed to recover the highly corrupted images. But the transform-based approaches are recovering more efficiently. So here the ADLWT is introduced with the Accelerated Proximal Gradient Line (APGL) optimization. It recovers the corrupted image in less time because the APGL is fast in computations.

The main contribution of the work are as follows

- An efficient Adaptive Directional Lifting based APGL approach has been introduced to improve diagonal correlation among the pixels.
- The interpolation method has been introduced to identify the diagonal relation between pixels. Then the predicted pixels are updated.
- The proposed method has been evaluated using FRIQA and NRIQA measures. The results are stating that the proposed method is recovering the highly corrupted image.

The paper has been organized as section 1 gives literature review on Image Completion methods. The previous works done are discussed, in Section 2 drafted with the earlier work done by various authors. Section 3 is provided with detail explanation of the ADL based optimization method to solve the optimization function. In section 4 presented the results on various recovered images. Finally, section 5 gives the conclusion on proposed method.

Literature Review

Image Completion is having the wide application scope in Machine Learning, Compressed Sensing and Computer Vision applications. The image completion is performed with the highly corrupted images. The conventional denoising algorithms are able to eliminate the noise in less corrupted images. The wavelets are playing a vital role in the denoising of an image. Recent years fully exploiting the directional correlation in either spatial or frequency domain with the directional filter banks. Most of the decomposition methods are become expensive systems and difficult for the applications, Daubechies et al., proposed lifting wavelet. It reduces the computational complexity of conventional wavelet transform. Adaptive directional lifting wavelet transform incorporates the local spatial prediction into each lifting step [4, 5]. The direct applying of ADL may lead of some artifacts in the recovered image.

The major problem in directional prediction with wavelet decomposition makes the conflict of global and local features. To eliminate the noise in highly corrupted images denoising methods are not sufficient. To get better quality in the image both denoising method and optimization need to be combined. The Singular Value Thresholding (SVT) is the most familiar method developed by E.J. Candes et al. [6]. The basic optimization function is formed as

$$\min_I \|I\|_* + \alpha\|I\|_F^2 \qquad Subject\ to\ P_\Omega(I) = P_\Omega(R) \qquad (1)$$

The eq. 1 is solved by the Uzawa method and solves efficiently. But the missing ratio in the image getting increase the existing methods are unable to recover. So a transformation based optimization need to introduced to recover the highly corrupted images. Y. Hu et al. [7] proposed rank minimization method which is able to recover better than the

SVT. The proposed algorithm is based on the rank, as the minimal rank is considered the recovered image will have the good measures. If the missing ratio in the image is increasing, the given method alone unable to recover the data. The objective function is formed as in eq.2

$\min_I \|I\|_r + \alpha\|I\|_F^2 \qquad Subject\ to\ P_\Omega(I) = P_\Omega(R)$ (2)

Wang Y et al. [8] proposed a transform-based optimization method which is used the TNNR as the special condition and achieved the good recovery of the image. The objective function is defined as

$\hat{X} = arg\min_I \|I\|_* + \sum_{i=1}^{s} \lambda_i \|I\|_{DCT}^{p_i,q_i} + \frac{\gamma}{2}\|P_\Omega(I) - P_\Omega(R)\|_F^2$ (3)

Jing dong et al [9], proposed a low rank based matrix completion induced with Discrete Cosine Transform (DCT). It recovers the image with high PSNR and high SSIM. Kumar J S et al. [10] proposed the method lifting based optimization named LwRM regularizer is able to recover the highly corrupted image. The problem is defined as in eq. 4

$\hat{I} = \arg min \|I\|_* + \lambda\|I\|_{LWT} + \frac{\gamma}{2}\|\mathcal{P}_\Omega(I) - \mathcal{P}_\Omega(R)\|_F^2$ (4)

They proposed with the most familiar gradient-based optimization. Here is used with the adaptive lifting wavelet transform. Nestrov [11] proposed an optimization method which has the fast convergence rate with less computational complexity. Here the Adaptive Directional Lifting is combined with the gradient descent-based optimization. The introduced method is evaluated with the most familiar metrics PSNR [12], SSIM [12], and NIQE [13]. The results are enclosed in section 5 and discussed in-detail.

ADLWT Regularizer

Here we are proposing a transform-based optimization method which can recovers the highly corrupted image. The adaptive directional lifting wavelet transform is used, because the corrupted pixel values are identified with help of directionally identified uncorrupted pixel values.

Adaptive Directional Lifting (ADL) Wavelet Transform

The Adaptive Lifting Wavelet performs the operations in horizontal and vertical directions. The Adaptive Directional Lifting is not limited to the horizontal and vertical directions the diagonal operation will be performed by considering the angle. The basic adaptive directional lifting performs the split, predict, update and normalize operations. It provides the sub-pixel perfect and accurate reconstruction of corrupted pixel value. The prediction of each is a linear combination of neighboring even coefficients with strong correlation in the concern directions. A high angular resolution in prediction is achieved by the use of the fractional pixels in prediction and update steps. An interpolation operation is attached to the prediction and update steps in the ADL scheme. The fig. 1 shows the sample directions of finding the pixels in different directions.

$X_e(m, n) = X(m, 2n)$

$X_o(m,n) = X(m,2n+1)$

$P_e[m,n] = \sum_i p_i x_e^*[m + i, n + sign(i-1) * dir]$

$U_d[m,n] = \sum_i u_i d^*\ [m + i, n + sign(i-1) * dir]$ (5)

P_e represents the lifting coefficient for prediction step and U_d represents the updation coefficients. Update process to replaces the pixel values identified using eq. 5. Every pixel/block have the transform direction the direction yielding the smallest high frequency energy is considered as transform direction. By using interpolation method, the effective direction will be calculated and with that updation will be done.

The SVD has been applied transformed image regions separately, then the unitary matrices and singular values are used in the optimization function as variables.

APGL Optimization Process

The optimization function can be described as eq. 6 and it is solved using the accelerated proximal gradient line method.

$\hat{I} = arg\min_I \|I\|_* + \lambda\|I\|_{ADL} + \frac{\gamma}{2}\|\mathcal{P}_\Omega(I) - \mathcal{P}_\Omega(R)\|_F^2$ (6)

Update I_{k+1}:

$I_{k+1} = \arg\min\|I\|_* + \frac{1}{2t}\|I - (I_k - t_k.\nabla f(I_k)\|_F^2$ (7)

Equation (21) can be solved using $U^T S V = I_k - t_k.\nabla f(I_k)$ and = max $((S_i - t_k), 0)$

Updatet_{k+1}:

$t_{k+1} = \frac{1+\sqrt{1+4t_k^2}}{2}$ (8)

Update R_{k+1}:

$R_{k+1} = I_{k+1} + \frac{t_k - 1}{t_{k+1}}(I_{k+1} - I_k)$ (9)

Algorithm

- Input: observed set *I, R*
- Initialization: The recovered Image *M=I, λ.*
- Apply the Adaptive Direction Lifting on each layer of the image then calculate the SVD of I_l
- Compute A_l and B_l from uniform matrix obtained from SVD
- Solve the following constrained optimization problem
- Until $\|I_{l+1} - I_l\|_F \leq 0.001$ if condition gets satisfied stop the iteration otherwise continue the iteration.

RESULTS AND DISCUSSION

The proposed ADLWRM is tested with the bench mark images [14]. The recovered images are evaluated with various image quality assessment metrics. The full reference image quality assessment metrics MSE, PSNR, and SSIM. The No-reference image quality assessment metric NIQE. The recovered results for the pepper image are shown in fig. 2. It clearly says that the recovery of the corrupted image has the best visual quality at λ=0.01 using the adaptive directional lifting scheme. Fig. 3 shows PSNR and SSIM of Pepper image recovered with different corrupted ratios and with different lambda values. The lambda value is 0.0001 the PSNR is more to recovered image with 10 % uncorrupted samples, but the SSIM value is very minimal. Because to the minimal lambda value the objective function is reaching the convergence faster and without recovering the corrupted observations it is reaching the stop condition. If we increase the number of iterations also it is providing the same result. To the lambda value 0.01 the PSNR and the SSIM values are providing the better results. Similarly, the NRIQA measure NIQE also minimal value for the lambda (0.01) as shown in fig. 4 (a). In fig. 4 (b) shows the time taken to recover the corrupted images with different stages. It varies from 10 % to 90% uncorrupted observations vs the time taken with different lambda values. The Tab.1(a) to (d) shows the numerical values of FRIQA (MSE, PSNR and SSIM) and NRIQA (NIQE) metrics for different missing ratios. Fig. 5 (a) to (d) shows the comparison graphs for the provided tables. The plotted graphs are clearly giving the hypothesis that the lambda value is the very important parameter in recovering the highly corrupted image.

CONCLUSION

The proposed ADLWT Regularizer is able to direct the subpixel position edge detail of the image properly with adaptive direction. In every stage of the missing ratio the proposed method can guaranteed the perfect recovery. To improve the efficiency of the method the optimization is combined, so it can be easily address image acquisition problems in the machine learning. The gradient method the ω is played a crucial role and the optimal value identified as 0.01. The FRIQA metrics PSNR, and SSIM are reported as 30.22dB and 0.8451 respectively to 80% corrupted image. Similarly, for the NRIQA metric NIQE as 9.52 and time taken to recover the corrupted image is 14.34 sec.

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Tab. 1 (a) Peak Signal to Noise Ratio vs Missing Ratio

Missing Ratio/ Lambda Value	10.00	20.00	30.00	40.00	50.00	50.00	70.00	80.00	90.00
0.0001	31.74	31.63	31.51	31.31	31.07	30.79	30.32	29.68	34.49
0.001	43.30	40.18	37.96	36.07	34.48	33.10	31.74	30.32	28.99
0.05	44.44	40.44	37.94	35.91	34.33	33.27	32.38	31.55	30.65
0.01	44.53	40.58	38.14	36.14	34.51	33.06	31.61	30.22	29.13
0.1	44.55	39.89	37.44	35.41	34.72	33.81	33.18	32.40	31.67

Tab. 1 (b) Structural Similarity for various lambda values

Missing Ratio/Lambda Value	10.00	20.00	30.00	40.00	50.00	60.00	70.00	80.00	90.00
0.0001	0.9517	0.9482	0.9433	0.9375	0.9286	0.9153	0.8935	0.8484	0.4025
0.001	0.9974	0.9939	0.9884	0.9797	0.9662	0.9477	0.9178	0.8617	0.7226
0.05	0.9978	0.9940	0.9866	0.9721	0.8940	0.7553	0.6264	0.4796	0.3394
0.01	0.9979	0.9943	0.9886	0.9798	0.9662	0.9469	0.9135	0.8451	0.6201
0.1	0.8693	0.7416	0.6354	0.6108	0.6738	0.5674	0.4734	0.3684	0.2769

Tab. 1 (c) NIQE for various lambda values

Missing Ratio/Lambda Value	10.00	20.00	30.00	40.00	50.00	50.00	70.00	80.00	90.00
0.0001	6.47	6.33	7.18	7.23	8.05	8.36	9.81	13.10	12.18
0.001	3.26	3.41	3.54	4.39	4.71	5.67	7.05	10.56	16.39
0.05	3.39	3.63	3.67	4.50	7.63	15.22	15.90	13.86	11.48
0.01	3.36	3.64	3.71	4.32	4.72	5.70	7.06	9.52	13.66
0.1	24.24	28.30	27.14	26.45	27.23	28.60	27.37	16.07	12.86

Tab. 1 (d) Time taken to recover the image

Missing Ratio/Lambda Value	10.00	20.00	30.00	40.00	50.00	50.00	70.00	80.00	90.00
0.0001	13.40	14.51	14.65	15.84	17.59	18.79	20.97	24.06	10.22
0.001	15.52	15.33	14.93	14.89	15.26	14.37	14.25	14.59	17.10
0.05	10.79	12.89	14.11	14.98	16.47	17.85	19.45	20.39	21.93
0.01	9.97	9.85	10.21	11.52	10.87	11.46	12.38	14.34	18.14
0.1	8.39	8.88	9.37	14.51	21.02	22.56	23.30	24.76	25.20

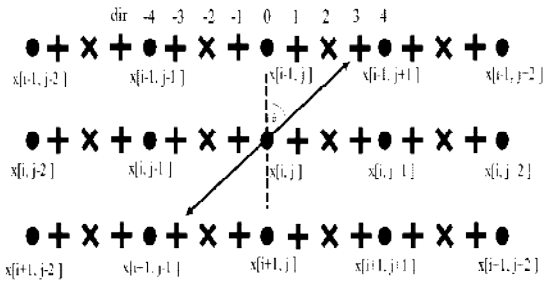


Fig. 1. Direction of sample collection

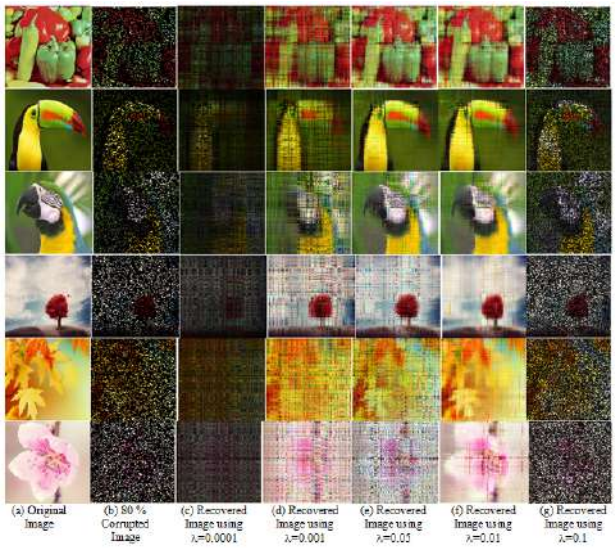
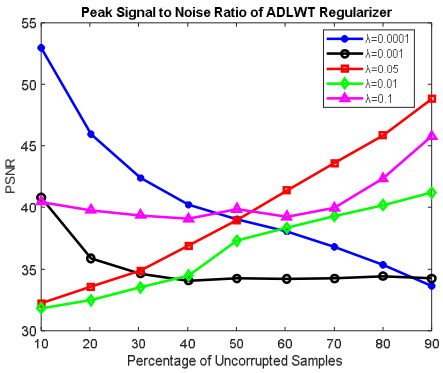
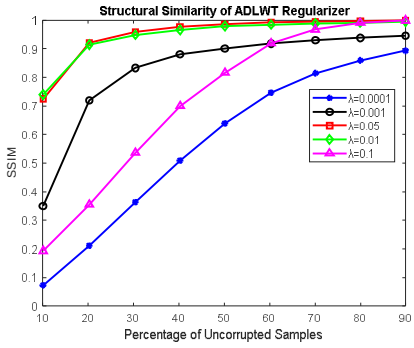


Fig. 2. Sample recovered image from the 80 % corrupted observations with different 'λ' values.

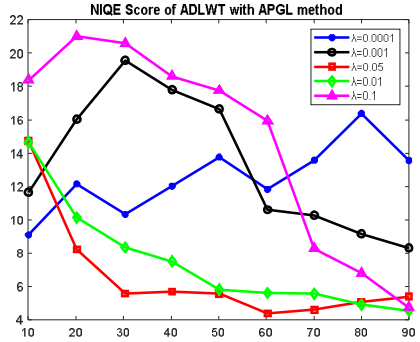


(a) Percentage of Uncorrupted Samples vs PSNR

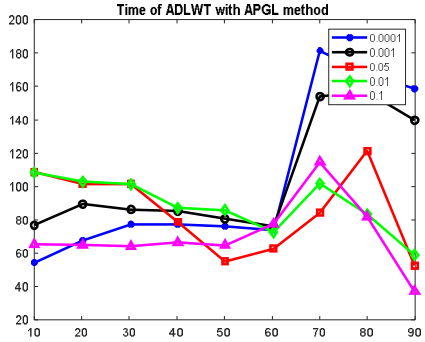


(b) Percentage of Uncorrupted Samples vs SSIM

Fig. 3. FRIQA metricsPSNR and SSIM of Pepper image for different values of λ



(a) Percentage of Uncorrupted Samples vs NIQE



(b) Percentage of Uncorrupted Samples vs time

Fig. 4. NRIQA metric NIQE of Pepper image for different values of λ

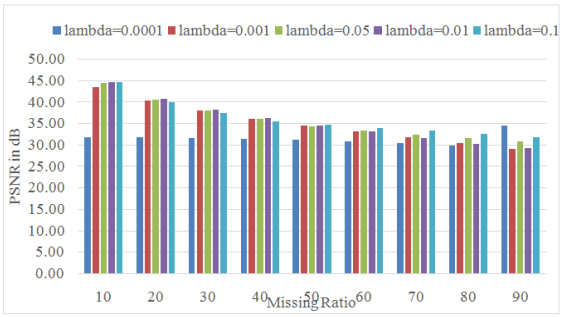


Fig. 5 (a) PSNR of Parrot image recovered from different missing ratios and different Lambda values

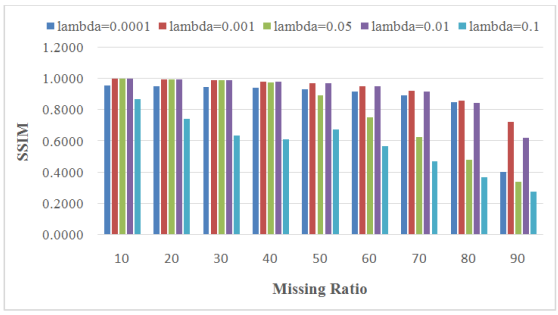


Fig. 5 (b) SSIM of Parrot image recovered from different missing ratios and different Lambda values

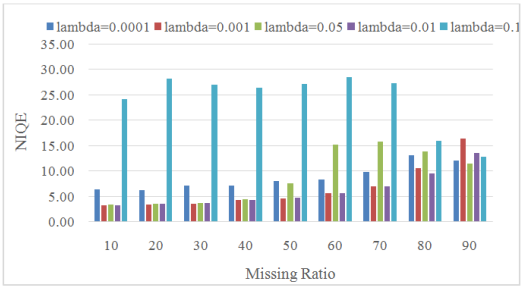


Fig. 5 (c) NIQE of Parrot image recovered from different missing ratios and different Lambda values

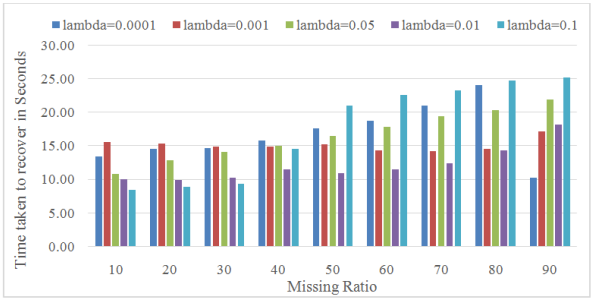


Fig. 5 (d) Time taken to recover parrot image from different missing ratios and different 'λ' values

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RESEARCH ARTICLE

A Study on the Effectiveness of Yogic Eye Exercises on Diminished Ophthalmic Vision among Patients with Myopia at Selected Eye Clinic, Puducherry

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ABSTRACT

In today's world, peoples spend much time in reading, writing, using of computer, watching television and mobile phones without an aware about the impacts of digital devices. It may cause eyes strains due to improper care and overuse of eyes. As the result, peoples have been affected with visual problems such as glaucoma, cataract, retinal problems, refractive error etc. Myopia is otherwise known as near-sightedness. Myopia occurs when the images focus in front of the retina. Yogic Eye Exercises have a great role in improving the visual acuity, reducing the asthenic symptoms and refraction by relaxing and strengthening the ocular muscle[1].Quantitative research approach and Pre-experimental one group pre-test and post-test design was conducted to assess the effectiveness of Yogic Eye Exercises on diminished ophthalmic vision among 113 Patients with Myopia at selected Eye Clinic, Puducherry by purposive sampling technique and data was collected by using clinical assessment of subjective criteria for myopia to assess Diminished Ophthalmic Vision. The data was analysed using both descriptive and inferential statistics SPSS software. Among 113 patients with myopia, diminished Ophthalmic Vision was improved from 3.17 with the Standard deviation of 0.62 to 2.19 with the standard deviation of 0.63 and it is statistically significant at the level of $p<0.001$.Association between the demographic variables with pre-test Diminished Ophthalmic Vision of patients with Myopia reveals that it was statistically found that the demographic variables has significant association on nature of work at the level of $P<0.05$.It indicates that the Yogic Eye Exercise was effective on reducing Diminished Ophthalmic Vision among patients with myopia.

Keywords: Myopia, Yogic eye exercise, diminished ophthalmic vision and near sightedness. :

INTRODUCTION

Eyes are an important part of our body. In worldwide, according to the Brien Holden Vision Institute**,** evidence is mounting that myopia is growing around the world with a recent study estimating that on average of 30% of the world is currently myopic and by 2050 based on current trends almost 50% will be myopic that is an estimated amount of 5 billion people around the world. The highest prevalence estimates for myopia for young adults in Asia estimates that 90% peoples were urbanized and highly educated populations. The crude prevalence of myopia in adults aged ≥40 years in USA, Western Europe and Australia was 25.4, 26.6 and 16.4%, respectively. In adults aged ≥40 years in East Asia, the prevalence tends to be higher than in other ethnic populations [2]. Sandra Jobke et.al., (2015) has conducted a study on the prevalence rates of refractive errors among children, adolescents, and adults in Germany. Quantitative research approach was adopted in this study. Purposive sampling method was used to select the study participants. This study concluded that the prevalence rates of myopia differed significantly between all investigated age groups: it was 0% in children aged 2–6 years, 5.5% in children aged 7–11 years, 21.0% in adolescents (aged 12–17 years) and 41.3% in adults aged 18–35 years. The prevalence of myopia in females (23.6%) was significantly higher than in males [3].

The most common symptom of myopia is blurred distance vision. Myopia can be evaluated through subjective assessment of symptoms, Snellen chart reading and refraction. Yogic Eye Exercises have a great role in improving the visual acuity, reducing the asthenopic symptoms and refraction by relaxing and strengthening the ocular muscle. According to the researcher view, many patients are affected with myopia and they are usually overcome using powerful glasses and lenses which correct the refractive errors of the eye. Eye exercises are improving the vision naturally. Researcher has an idea to implement these exercises in my area and provide awareness about natural method of vision improvement [4].

METHODS AND MATERIALS

Quantitative research approach and Pre-experimental one group pre-test and post-test design was conducted to assess the effectiveness of Yogic Eye Exercises on diminished ophthalmic vision among Patients with Myopia at selected Eye Clinic, Puducherry. 113 patients with myopia were selected by purposive sampling technique and data was collected by using clinical assessment of subjective criteria for myopia to assess Diminished Ophthalmic Vision. Patients those who are all coming under the age group of early adult with the age group between18-35 years were included in the study. Tools to assess the diminished ophthalmic vision was demographic variables and clinical assessment of subjective criteria for myopia and it has 4 options such as almost constant (4), frequent blurring of vision (3), occasional blurring of vision and no blurring of vision(1). Pre-test were conducted and after that yogic eye exercises were teaches and practiced by the patients for the 30 continues days (Twice in a day) and post-test was conducted with the same subjective criteria. The data was analysed using both descriptive and inferential statistics SPSS software.

RESULTS AND DISCUSSION

Frequency and percentage wise distribution of demographic variables among patients with myopia shows that majority of them were 59(52.2%) belongs to the age group of 18-23 years, 63(55.8%) of them were belongs to female, 84(74.3%) of them were hindu, 54(47.8%) of them were graduate and above, 63(55.8%) were having family history of refractive error, 61(54%) were watching TV above 3 years and 93(82.3%) were had the history of using computer/ video games/phones. Frequency and percentage wise distribution on Diminished Ophthalmic Vision among patients with myopia reveals that out of 113 study participants in pre-test, 14(12.4%) of the study participants were with occasional blurring of vision, 66(58.4%) of the study participants were with frequent blurring of vision and 33(29.2%) of the study participants were with almost constant blurring of vision whereas in post-test, 14(12.4%) of the study

participants were with no blurring of vision, 63(55.8%) of the study participants were with occasional blurring of vision, 36(31.9%) of the study participants were with frequent blurring of vision and none of them of the study participants were with almost constant blurring of vision. Diminished Ophthalmic Vision was improved from 3.17 with the Standard deviation of 0.62 to 2.19 with the standard deviation of 0.63 and it is statistically significant at $p<0.001$. It indicates that the Yogic Eye Exercise was effective on reducing Diminished Ophthalmic Vision among patients with myopia. Association between the demographic variables with pre-test Diminished Ophthalmic Vision of patients with Myopia reveals that it was statistically found that the demographic variables has significant association on nature of work at the level of $P<0.05$.

This result was supported by G.Gopinath et.al., (2012) has conducted a Clinical Study to Evaluate the Efficacy of Yoga Eye Exercises in the Management of myopia. The clinical study was done on 66 patients selected by random sampling technique. Yoga eye exercises were given for 6 weeks. Assessment was based on signs and symptoms of disease and all the objective parameters like retinoscopy, autorefractometer, keratometer were adopted. This study shows that markedly improved and moderate improvement was observed in one patient (3.20%), mild improvement was observed in 20 patients (64.45%), and no improvement was observed in 10 patients (32.25%) [5].

CONCLUSION

A study on Effectiveness of Yogic Eye Exercise on diminished ophthalmic vision among Patients with Myopia at selected Eye clinic, Puducherry. The findings of the study revealed that there were improved visual parameters among patients with myopia who received Yogic Eye Exercises for the 6 weeks in 45 early morning sessions.

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Table 1:Frequency and percentage wise distribution on Diminished Ophthalmic Vision among patients with myopia (n=113)

S.NO	Diminished Ophthalmic Vision	PRETEST		POSTTEST	
		f	%	f	%
1.	No blurring of vision	0	0	14	12.4
2.	Occasionally	14	12.4	63	55.8
3.	Frequently	66	58.4	36	31.9
4.	Almost constantly	33	29.2	0	0

Table–2: Comparison between pre-test and post-test on Diminished Ophthalmic Vision among patients with myopia (n=113)

	MEAN	S.D	't' TEST	'P' VALUE
Pre-test	3.17	0.62	41.62	0.001*
Post-test	2.19	0.63		

-p<0.05, significant and **-p<0.001, highly significant

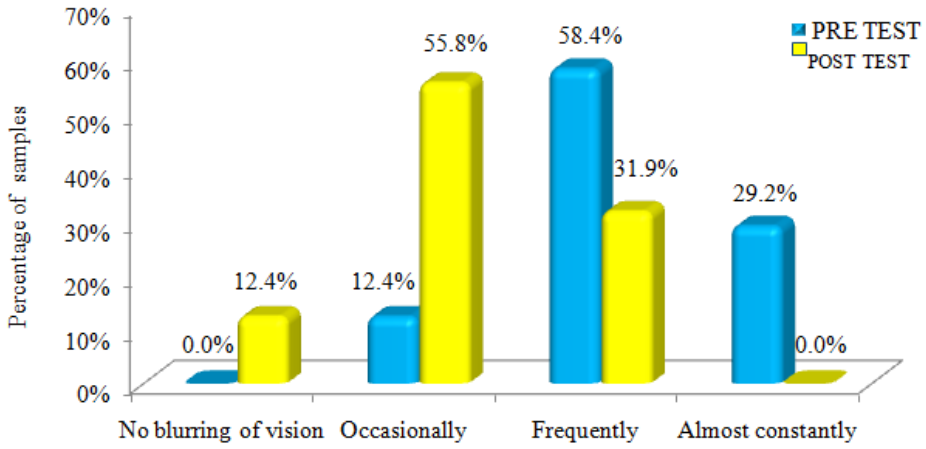

Fig.1. Bar Diagram showing Percentage wise distribution on diminished ophthalmic vision among patients with myopia.

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RESEARCH ARTICLE

Some Contributions of (1,2)*-$\widehat{D}$-Closed Sets in Bitopological Spaces

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ABSTRACT

In the paper,we introduce the notion of(1,2)*-$\widehat{D}$-cld sets and (1,2)*-D-cld sets in bitopological spaces.

2010 Mathematics Subject Classification: 54E55
Keywords: (1,2)*-D-cld, (1,2)*-$\widehat{D}$-cld, (1,2)*-$\widehat{D}$-open, (1,2)*-D-open.

INTRODUCTION

J. C. Kelly [3],the introduced the bitopological spaces andK. Dass and G. Suresh [2], introduced the$\widehat{D}$-closed sets in topological spaces. The study of generalized closed sets in a topological space was initiated by Levine [4]. In 2012, J. Antony Rex Rodrigo and K. Dass [1], the introduced the concept of D-closed sets and their properties. S. Pious Missier, et al.[5], the introduced the on contra-continuous functions and strongly r closed spaces. In the paper, we introduce the notion of (1,2)*-$\widehat{D}$-closed sets and (1,2)*-D-closed sets in bitopological spaces.

PRELIMINARIES

Throughout this paper $(X, \tau_{1,2})$ or X will always denote bitopological spaces When A is a subset of $\tau_{1,2}$-cl(A) and $\tau_{1,2}$-int(A) denote the $\tau_{1,2}$-closure and $\tau_{1,2}$-interior set of A respectively.

We recall some known definitions are needed in the paper.

Definition 2.1 Let A be a subset of X. Then A is said to be $\tau_{1,2}$-open [8] if $H = P \cup Q$ where $P \in \tau_1$ and $Q \in \tau_2$.

The complement of $\tau_{1,2}$-open set is called $\tau_{1,2}$-closed.

Notice that $\tau_{1,2}$-open sets need not necessarily form a topology.

Definition 2.2 [8]Let A be a subset of X. Then

(i) the $\tau_{1,2}$-closure of A, denoted by $\tau_{1,2}$-cl(A), is defined as $\cap \{F : A \subseteq F \text{ and } F \text{ is } \tau_{1,2}\text{-closed}\}$.

(ii) the $\tau_{1,2}$-interior of A, denoted by $\tau_{1,2}$-int(A), is defined as $\cup \{F : F \subseteq A \text{ and } F \text{ is } \tau_{1,2}\text{-open}\}$.

Definition 2.3 A subset A of X, is called

[1] a (1,2)*-pre-open [7] if $A \subseteq \tau_{1,2}\text{-int}(\tau_{1,2}\text{-cl}(A))$;

[2] a (1,2)*-semi-open [7] if $A \subseteq \tau_{1,2}\text{-cl}(\tau_{1,2}\text{-int}(A))$;

[3] a (1,2)*-α-open [6] of $A \subseteq \tau_{1,2}\text{-int}(\tau_{1,2}\text{-cl}(\tau_{1,2}\text{-int}(A)))$;

[4] a (1,2)*-semi-pre-open[8] (=(1,2)*-β-open) if $A \subseteq \tau_{1,2}\text{-cl}(\tau_{1,2}\text{-int}(\tau_{1,2}\text{-cl}(A)))$;

[5] a regular (1,2)*-open [9] $A=\text{int}(\text{cl}(A))$;

The complement of the above open sets iscalled closed sets respectively (briefly, (1,2)*-pre-cld, (1,2)*-semi-cld, (1,2)*-α-cld, (1,2)*-semi-pre-cld, regular (1,2)*-cld).

Definition 2.4 A subset A of X, is called

[1] a (1,2)*-generalized closed (briefly, (1,2)*-g-cld) [12] if $\tau_{1,2}\text{-cl}(A) \subseteq U$ whenever $A \subseteq U$ and U is $\tau_{1,2}$-open;

[2] a (1,2)*-generalized semi-preclosed (briefly, (1,2)*-gsp-cld)[7] if $(1,2)^*\text{-spcl}(A) \subseteq U$ whenever $A \subseteq U$ and U is $\tau_{1,2}$-open;

[3] a (1,2)*-regular generalized closed (briefely, (1,2)*-rg-cld) [8] if $\tau_{1,2}\text{-cl}(A) \subseteq U$ whenever $A \subseteq U$ and U is regular (1,2)*-open;

[4] a (1,2)*-generalized pre-regular closed (briefely, (1,2)*-gpr-cld) [7] if $(1,2)^*\text{-pcl}(A) \subseteq U$ whenever $A \subseteq U$ and U is regular (1,2)*-open;

[5] a (1,2)*-ω-closed [11] (briefly, (1,2)*-ω-cld,=(1,2)*-$\hat{g}$-cld) if $\tau_{1,2}\text{-cl}(A) \subseteq U$ whenever $A \subseteq U$ and U is (1,2)*-semi-open;

[6] a (1,2)*-*g-closed(briefly, (1,2)*-*g-cld)[10] if $\tau_{1,2}\text{-cl}(A) \subseteq U$ whenever $A \subseteq U$ and U is (1,2)*-ω-open;

[7] a (1,2)*-g*-closed (briefly, (1,2)*-g*-cld) [11] if $\tau_{1,2}\text{-cl}(A) \subseteq U$ whenever $A \subseteq U$ and U is (1,2)*-g-open;

[8] a (1,2)*-g*p-closed (briefly, (1,2)*-g*p-cld) [11] if $(1,2)^*\text{-pcl}(A) \subseteq U$ whenever $A \subseteq U$ and U is (1,2)*-g-open;

[9] a (1,2)*-α*g-closed (briefly, (1,2)*-α*g-cld) [6] if $(1,2)^*\text{-}\alpha\text{cl}(A) \subseteq U$ whenever $A \subseteq U$ and U is (1,2)*-ω-open;

[10] a (1,2)*-*gs-closed(briefly, (1,2)*-*gs-cld) [7] if $(1,2)^*\text{-scl}(A) \subseteq U$ whenever $A \subseteq U$ and U is (1,2)*-ω-open;

[11] a (1,2)*-pre-semi-closed(briefly, (1,2)*-pre-semi-cld) [7] if $(1,2)^*\text{-spcl}(A) \subseteq U$ whenever $A \subseteq U$ and U is (1,2)*-g-open;

[12] a (1,2)*-gspr-closed(briefly, (1,2)*-gspr-cld) [12] if $(1,2)^*\text{-spcl}(A) \subseteq U$ whenever $A \subseteq U$ and U is regular-(1,2)*-open;
The complement of the above closed sets iscalled open sets.

BASIC PROPERTIES OF (1,2)*-$\hat{D}$-CLOSED SETS

Definition 3.1A subset A of X is called a

(i) (1,2)*-D-closed(briefly, (1,2)*-D-cld) if $(1,2)^*\text{-scl}(A) \subseteq \tau_{1,2}\text{-int}(U)$ whenever $A \subseteq U$ and U is (1,2)*-ω-open;

(ii) (1,2)*-$\hat{D}$-closed (briefly, (1,2)*-$\hat{D}$-cld) if $(1,2)^*\text{-spcl}(A) \subseteq U$ whenever $A \subseteq U$ and U is (1,2)*-D-open;

The class of all (1,2)*-$\hat{D}$-cld in X is denoted by (1,2)*-$\hat{D}$C.

Properties 3.2 Every $\tau_{1,2}$-closed (resp. (1,2)*-α-cld, (1,2)*-pre-cld, (1,2)*-semi-cld) is (1,2)*-$\hat{D}$-cld.

Proof. Let A be any $\tau_{1,2}$-closed set. Let $A \subseteq U$ and U is (1,2)*-D-open set in X. Then $\tau_{1,2}$-cl(A)⊆U. But (1,2)*-spcl(A)⊆$\tau_{1,2}$-cl(A)⊂U. Thus A is (1,2)*-$\hat{D}$-cld. The proof follows from the facts that(1,2)*-spcl(A)⊆(1,2)*-scl(A)⊆$\tau_{1,2}$-cl(A) and (1,2)*-spcl(A)⊆(1,2)*-pcl(A)⊆(1,2)*-αcl(A)⊆$\tau_{1,2}$-cl(A).

Remark 3.3 The converse of the above theorem need not be true.

Example3.4 Let $X=\{m,n,o,p,q\}$ with $\tau_1=\{\phi,\{m\},\{m,n\},X\}$ and $\tau_2=\{\phi,\{o,p\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{m,n\},\{o,p\},\{m,o,p\},\{m,n,o,p\},X\}$. Here, $J=\{m,n,p\}$ is (1,2)*-$\hat{D}$-cld (resp. not (1,2)*-pre-cld, not (1,2)*-α-cld, not (1,2)*-semi-cld).

Properties 3.5 Every (1,2)*-$\hat{D}$-cld is (1,2)*-gspr-cld

Proof. Let A be any (1,2)*-$\hat{D}$-cld set. Let $A \subseteq U$ and U is regular (1,2)*-open in X. Since every regular (1,2)*-open set is $\tau_{1,2}$-open and every $\tau_{1,2}$-open is (1,2)*-D-open, we get (1,2)*-spcl(A)⊆U. Hence A is (1,2)*-gspr-cld.

Remark 3.6 The converse of the above theorem need not be true.

Example 3.7 Let $X=\{m,n,o,p\}$ with $\tau_1=\{\phi,\{m\},\{n\},\{m,n\},X\}$ and $\tau_2=\{\phi,\{p\},\{n,p\},X\}$.

The $\tau_{1,2}=\{\phi,\{m\},\{n\},\{p\},\{m,n\},\{n,p\},\{m,p\},\{m,n,p\},X\}$.Here, $J=\{m,n,p\}$ is (1,2)*-gspr-cld but not (1,2)*-$\hat{D}$-cld.

Theorem 3.8. Every (1,2)*-ω-cld is (1,2)*-$\hat{D}$-cld.

Proof. Let A be (1,2)*-ω-cld in X. Let $A \subseteq U$ and U is (1,2)*-D-open. Then $\tau_{1,2}$-cl(A)⊆U. Since every (1,2)*-ω-cld set is (1,2)*-pre-cld and every (1,2)*-pre-cld set is (1,2)*-semi-pre-cld, A is (1,2)*-semi-pre-cld.
Then A⊆(1,2)*-pcl(A)⊆(1,2)*-ωcl(A), Since every $\tau_{1,2}$-closed is (1,2)*-ω-cld, (1,2)*-ω-cl(A)⊆$\tau_{1,2}$-cl(A).Therefore, (1,2)*-spcl(A)⊆(1,2)*-pcl(A)⊆$\tau_{1,2}$-cl(A)⊆U. Hence A is (1,2)*-$\hat{D}$-cld.

Remark 3.9 The converse of the above theorem need not be true.

Example 3.10 Let $X=\{m,n,o\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{n\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{n\},\{m,n\},X\}$. Here,J ={m} is (1,2)*-$\hat{D}$-cld but not (1,2)*-ω-cld.

Proposition 3.11 Every (1,2)*-$\hat{D}$-cld is (1,2)*-gsp-cld.

Proof. Let A be any (1,2)*-$\hat{D}$-cld in X. Let $A \subseteq U$ and U is $\tau_{1,2}$-open set in X. Since every $\tau_{1,2}$-open is (1,2)*-D-open, we get (1,2)*-spcl(A)$\subseteq$U. Hence A is (1,2)*-gsp-cld.

Remark 3.12 The converse of the above theorem need not be true.

Example 3.13 Let $X=\{m,n,o\}$ with $\tau_1=\{\phi,X\}$ and $\tau_2=\{\phi,\{m\},X\}$. Then $\tau_{1,2}=\{\phi,\{m\},X\}$. Here, $J=\{m,n\}$ is (1,2)*-gsp-cld but not (1,2)*-$\hat{D}$-cld.

Proposition 3.14 Every (1,2)*-$\hat{D}$-cld is (1,2)*-pre-semi-cld

Proof. Let A be any (1,2)*-$\hat{D}$-cld in X. Let $A \subseteq U$ and U is (1,2)*-g-open in X. Since every (1,2)*-g-open is (1,2)*-D-open, we get (1,2)*-spcl(A)$\subseteq$U. Hence A is (1,2)*-pre-semi-cld.

Remark 3.15 The converse of the above theorem need not be true.

Example3.16 Let $X=\{m,n,o,p\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{m,n,o\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{m,n,o\},X\}$. Here, $J=\{m,n,o,p\}$ is (1,2)*-pre-semi-cld but not (1,2)*-$\hat{D}$-cld.

Remark 3.17 (1,2)*-$\hat{D}$-clossedness and (1,2)*-rg-closedness are independent.

Example 3.18 Let $X=\{m,n,o\}$ with $\tau_1=\{\phi,\{m\},X\}$ and

$\tau_2=\{\phi,\{n\},X\}$. Then $\tau_{1,2}=\{\phi,\{m\},\{n\},\{m,n\},X\}$. Here, $J=\{m\}$ is (1,2)*-$\hat{D}$-cld but not (1,2)*-rg-cld and set $K=\{m,n\}$ is (1,2)*-rg-cld but not (1,2)*-$\hat{D}$-cld.

Remark 3.19 (1,2)*-$\hat{D}$-closedness and (1,2)*-gpr-closedness are independent.

Example 3.20 Let $X=\{m,n,o\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{n\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{n\},\{m,n\},X\}$. Here, $J=\{m\}$ is (1,2)*-$\hat{D}$-cld but not (1,2)*-gpr-cld and the set $K=\{m,n\}$ is (1,2)*-gpr-cld but not (1,2)*-$\hat{D}$-cld.

Remark 3.21 (1,2)*-$\hat{D}$-closedness and (1,2)*-g-closedness are independent.

Example 3.22 Let $X=\{m,n,o,p\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{m,n,o\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{m,n,o\},X\}$. Here, J={n} is (1,2)*-$\hat{D}$-cld but not (1,2)*-g-cld and the set K={m,n,o} is (1,2)*-g-cld but not (1,2)*-$\hat{D}$-cld.

Remark 3.23 (1,2)*-$\hat{D}$-closedness and (1,2)*-D-closedness are independent.

Example 3.24 Let $X=\{m,n,o,p\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{m,n,o\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{m,n,o\},X\}$. Here,J={m,p} is (1,2)*-D-cld but not (1,2)*-$\hat{D}$-cld.

Example 3.25 Let $X=\{m,n,o\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{n\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{n\},\{m,n\},X\}$. Here,J={m} is (1,2)*-$\hat{D}$-cld but not (1,2)*-D-cld.

Remark 3.26 (1,2)*-$\hat{D}$-closedness and (1,2)*-*g-closedness are independent.

Example 3.27 Let $X=\{m,n,o,p\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{m,n,o\},X\}$. Then $\tau_{1,2}=\{\phi,\{m\},\{m,n,o\},X\}$. Here,J={m,n,p} is (1,2)*-*g-cld but not (1,2)*-$\hat{D}$-cld.

Example 3.28 Let $X=\{m,n,o\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{n\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{n\},\{m,n\},X\}$. Here,J={m} is (1,2)*-$\hat{D}$-cld but not (1,2)*-*g-cld.

Remark 3.29 (1,2)*-$\hat{D}$-closedness and (1,2)*-g*-closedness are independent.

Example 3.30 Let $X=\{m,n,o,p\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{m,n,o\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{m,n,o\},X\}$. Here,J={m,o,p} is (1,2)*-g^* cld but not (1,2)*-$\hat{D}$-cld.

Example 3.31 Let $X=\{m,n,o\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{n\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{n\},\{m,n\},X\}$. Here,J={m} is (1,2)*-$\hat{D}$-cld but not (1,2)*-g*-cld.

Remark 3.32 (1,2)*-$\hat{D}$-closedness and (1,2)*-g*p-closedness are independent.

Example 3.33 Let $X=\{m,n,o,p\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{m,n,o\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{m,n,o\},X\}$. Here,J={m,p} is (1,2)*-g*p-cld but not (1,2)*-$\hat{D}$-cld.

Example 3.34 Let $X=\{m,n,o\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{n\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{n\},\{m,n\},X\}$. Here,J={m} is (1,2)*-$\hat{D}$-cld but not (1,2)*-g^*-cld.

Remark 3.35 (1,2)*-$\hat{D}$-closedness and (1,2)*-α*g-closedness are independent.

Example 3.36 Let $X=\{m,n,o,p\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{m,n,o\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{m,n,o\},X\}$. Here,J={m,p} is (1,2)*-α*g-cld but not (1,2)*-$\hat{D}$-cld.

Example 3.37 Let $X=\{m,n,o,p\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{m,n,o\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{m,n,o\},X\}$. Here,J={m,p} is (1,2)*-α*g-cld but not (1,2)*-$\hat{D}$-cld.

Remark 3.38 (1,2)*-$\hat{D}$-closedness and (1,2)*-*gs-closedness are independent.

Example 3.39 Let $X=\{m,n,o,p\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{m,n,o\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{m,n,o\},X\}$. Here,J={m,p} is (1,2)*-*gs-cld but not (1,2)*-$\hat{D}$-cld.

Example 3.40 Let $X=\{m,n,o\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{n\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{n\},\{m,n\},X\}$. Here,J={m} is (1,2)*-$\hat{D}$-cld but not (1,2)*-*gs-cld.

Remark 3.41(1,2)*-$\hat{D}$-closedness and (1,2)*-gp-closedness are independent.

Example 3.42 Let $X=\{m,n,o\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,X\}$. Then $\tau_{1,2}=\{\phi,\{m\},X\}$. Here, J={m,n} is(1,2)*- gp-cld but not (1,2)*-$\hat{D}$-cld.

Example 3.43 Let $X=\{m,n,o\}$ with $\tau_1=\{\phi,\{m\},X\}$ and $\tau_2=\{\phi,\{n\},X\}$.

Then $\tau_{1,2}=\{\phi,\{m\},\{n\},\{m,n\},X\}$. Here,J={m} is (1,2)*-$\hat{D}$-cld but not (1,2)*-gp -cld.

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RESEARCH ARTICLE

Role of Super Disintegrants on Rapid Release of the Drug Substance

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ABSTRACT

Separating of oral solid estimations structures which contain drugs that disintegrate absolutely in the oral pit inside one second. As tableting will turn out to be more noticeable further evolved, formulators slant toward direct pressing factor blends. Superdisintegrants further create disintegrating capability and decrease use levels appeared differently in relation to traditional disintegrants. Superdisintegrants are used to chip away at the practicality of solid estimations structures. This is refined by decreasing the separating time which consequently updates drug breaking down rate. Disintegrants are substances or mix of substances added the prescription enumerating that works with the detachment or separating of tablet or case content into more unassuming particles that deteriorate more rapidly than without disintegrants. Superdisintegrants are generally used at a low level in the solid portion structure, typically 1-10 % by weight relative with the outright weight of the portion unit. The orodispersible tablets get rapidly separate in the oral pit, they needn't mess with any need of gnawing and water. The critical part present in the orodispersible tablets are the superdisintegrants. The superdisintegrants are those experts which help to deal with the weakening of the tablet. There are different classes of superdisintegrants used in the speedy disintegrating or oral multifunctional superdisintegrants, etc This review includes the different kinds of superdisintegrants, their framework, their properties and ideal characters The present survey contains the various kinds of superdisintegrants which are being used in the definition to give the safer, convincing medicine movement with patient's consistence.

Keywords: superdisintegrants, natural, synthetic, co-processed, superdisintegrants techniques.

INTRODUTION [1-9]

One of the important drug delivery route for the drug administration is the oral route. So through this route the oral tablets can be administered Strong dose structures are notable due to their precise dosing, better tolerant consistence, self prescriptions and furthermore simplicity of organization. The orally crumbling tablets can be successfully utilized. They can give a preferred presentation over the ordinary tablets. Orodispersible tablets get deteriorate on the buccal mucosa of patient. So the orodispersible tablet is an original medication conveyance framework which giving a superior patient consistence or acknowledgment. It can likewise be utilized as a superior option for other oral meds. Tablet crumbling has gotten extensive consideration as a fundamental stage in acquiring quicker medication discharge. The accentuation on the accessibility of the medication features the significance of the generally fast crumbling of a tablet as a rule for guaranteeing uninhibited medication disintegration conduct. Various variables influence the crumbling conduct of tablets. The improvement of quick dissolving or breaking down tablets gives a chance to consider the job of disintegrants. As of late, synthetically altered disintegrants named as superdisintegrants have been created to further develop the crumbling measures. Determination of proper definition excipients and producing innovation can acquire the plan component of quick breaking down tablet. The disintegrants have the significant capacity to go against the effectiveness of the tablet cover and the actual powers that demonstration under pressure to frame the tablet. The more grounded the folio, the more powerful should be the deteriorating specialists all together for the tablet to deliver its drug. In a perfect world, it should make the tablet disturb, not just into the granules from which it is packed, yet in addition into powder particles from which the granulation is ready. The appropriate decision of a disintegrant or a super disintegrant and its comprise execution are of basic significance to the detailing advancement of such tablets. Medication discharge from a strong dose structure can be upgraded by expansion of reasonable disintegrants. In later years, expanding consideration has been paid to defining not just fast dissolving and additionally crumbling tablets that are gulped, yet additionally orally breaking down tablets that are expected to break down as well as deteriorate quickly in the mouth. An ideal disintegrant ought to have helpless solvency, helpless gel arrangement, great hydration limit, great compressibility, stream properties and no inclination to frame edifices with the medications.

SUPERDISINTEGRANTS [10-12]

In dispersible tablets, disintegrants assumes a significant part. Deteriorating specialists are substances regularly remembered for the tablet definitions to support the separation of the compacted mass when it is placed into a liquid climate. They advance dampness infiltration and scattering of the tablet network. As of late, a few more current specialists have been created known as "Superdisintegrants". These more current substance are more viable at lower fixations with more noteworthy breaking down productivity and mechanical strength. On contact with water the superdisintegrants grow, hydrate, change volume or frame and give further developed compressibility, similarity and contrarily affect the mechanical strength of definitions containing high-portion. Superdisintegrants can be considered as a primary weakener which helps in breaking down of strong measurements structures. At the point when the dose structure get presented to the wet climate, they get genuinely scattered inside the measurements structure and will extend. These particles are additionally compressible which assists with further developing tablet hardness and friability. The superdisintegrants give compressibility, similarity in a further developed way and they show no adverse consequence on the mechanical strength of plans containing high portion drugs.

THE IDEAL CHARACTERISTICS OF SUPERDISINTEGRANTS [13-14]

- Accelerate disintegrating process
- Compact to produce less friable tablets
- Effective at low concentration
- Have greater disintegrating efficiency
- Poor water solubility but good hydration ability
- Poor gel formation

- Good compressibility
- Inert
- Non-toxic
- Good flow properties
- Requirement of least quantity
- Good mouth feel
- Particle size

MODES OF ADDITION OF SUPERDISINTEGRANTS [15-17]

INTERNAL ADDITION [15]

In wet granulation strategy, the disintegrant is added to other excipients prior to wetting the powder with the grinding liquid. In this manner, the disintegrant is consolidated inside the granules. In dry granulation strategy, prior to compacting the powder between the rollers. croscarmellose sodium, intragranularly, extra granularly or disseminated similarly between the two periods of a tablet where an inadequately dissolvable medication established essentially 92.5% of the detailing. The outcomes investigated through an overall quadratic reaction surface model recommend that, tablets with a similar all out centralization of crosscarmellose sodium disintegrate at a quicker rate when the super disintegrant is incorporated intragranularly. Tablet friability isn't influenced by the technique for disintegrant joining.

EXTERNAL ADDITION [16]

Each wet and dry granulation method, the granules during dry blending preceding pressure. The impact of method of fuse of superdisintegrants (croscarmellose sodium, sodium starch glycolate and crospovidone) on disintegration of three model medications with shifting watery solvency (carbamazepine, acetaminophen and cetrizine HCl) from their particular tablet plans by wet granulation was examined. It is demonstrated that crospovidone is viable in working on the disintegration of the medications in extra granular method of expansion is by all accounts the best method of joining, regardless of the solvency of the principle tablet part.

INTERNAL AND EXTERNAL ADDITION [17]

In this strategy, disintegrant is isolated into two segments. One part is added before granule development (intra) and remaining piece is added to granules (extra) with blending preceding pressure. This strategy can be more successful. the granules further crumble by intra-granular piece to deliver the medication substance into arrangement. Nonetheless, the piece of intra-granular disintegrant (in wet granulation measures) is normally not really that compelling of extra-granular because of the way that it is presented to wetting and drying (as a feature of the granulation cycle) which diminishes the action of the disintegrant.

ADVANTAGES OF SUPERDISINTEGRANTS [18-20]

The employments of superdisintegrants are reached out inside the applications of prompt delivery tablets, oral breaking down tablets, quick dispersible tablets, containers, mouth-dissolving films, and so on

- Remarkable inclination on wetting causing quick breaking down
- No knot development on breaking down
- Compatible with usually utilized restorative specialists and excipients.
- Work similarly powerful in hydrophilic and hydrophobic plans.
- Provides great mechanical solidarity to the tablet working with simple pressing and transportation.
- Does not stay with the punches and colors.
- Although there are numerous superdisintegrants, which show unrivaled deterioration, the search for more current disintegrants is progressing and analysts are trying different things with changed normal items.

MECHANISM OF SUPERDISINTEGRANTS [21-32]

- Swelling.
- Porosity and capillary action (wicking).
- Combination action.
- Heat of wetting.
- Deformation.
- Enzymatic reaction.
- Electrostatic repulsion.
- Chemical reaction.

SWELLING [21-22]

Swelling is the most notable arrangement of both customary and designed superdisintegrants to cause tablet disintegrating. As the tablet connects with sensible medium, passage of water is the extraordinary fundamental development for this part followed by growing of the disintegrant atom which prompts improvement of broadening power achieve breakdown of tablet as shown in figure 1

WICKING (POROSITY AND CAPILLLARY ACTION) [23-24]

Disintegrating of tablet occurs by passageway of medium into the tablet and overriding the adsorbed air on the particles achieves weakening of intermolecular bond and breakdown of tablets into its fine particles. Figure 1 is shows the nuances of wicking arrangement of tablet disintegrating. Here, hydrophilic property of the drug and excipient close by tableting conditions chooses the water take-up of tablet. For making a hydrophilic association across drug particles, backing of porous development and low interfacial pressing factor towards watery fluid is indispensable.

COMBINATION ACTION [25]

In this instrument, the blend of both wicking and growing movement to separating.

HEAT OF WETTING [26-27]

When disintegrants with exothermic properties get wetted, restricted pressing factor is made due to hair like air augmentation, which supports separating of tablet. This explanation, regardless, is confined to two or three kinds of disintegrants and can't portray the movement of most present day disintegrating subject matter experts.

CHEMICAL REACTION (ACID-BASE REACTION) [28-29]

The tablet is quickly self-destructed by inside opportunity of CO_2 in water on account of association between tartaric destructive and citrus extricate (acids) with stomach settling agent metal carbonates or bicarbonates (bases) in presence of water. The tablet weakens in view old enough of squeezing factor inside the tablet. As a result of opportunity in CO_2 gas, the breaking down of dynamic medication trimmings in water similarly as taste covering sway is redesigned. As these disintegrants are significantly delicate to little changes in tenacity level and temperature, serious control of environment is required during preparation of the tablets. The effervescent blend is either added immediately going before pressure or can be incorporated two separate piece of itemizing.

DEFORMATION RECOVERY [30]

Deformation recovery theory induces that the condition of disintegrant particles is mangled during pressure and the particles return to their pre-pressure shape subsequent to wetting, thusly this extension in size of the contorted particles making the tablet self-destruct. Such a wonder may be a critical piece of the part of action of disintegrants, for instance, Crospovidone and starch that show for all intents and purposes no growing. Fig. 2 blueprints the shock and misshapening framework in tablet decay.

ENZYMATIC REACTION [31]

Synthetic substances available in the body furthermore go about as disintegrants. These synthetics circle back to limiting movement of folio and helps in separating. In light of amplifying, pressure is applied the outside way that makes the tablet division or burst. The accelerated maintenance of water prompts a huge extension in the volume of granules to propel disintegration i.e growing applies the squeezing factor towards the outside course, which makes the tablet break and helps in overhauling the water ingestion.

ELECTROSTATIC REPULSION [32]

This is another process for disintegrating that undertakings to elucidate the augmenting of tablet made with non-swellable disintegrants. Guyot-Hermann's has proposed an atom – particle shock theory reliant upon the discernment that non growing particle also cause weakening of tablets. The electric horrible forces between particles are the instrument of disintegrating and water is required for it. The water enters between starch grains because of its prejudice for starch surfaces, in this way breaking hydrogen bonds and various forces holding the tablet together.

SELECTION OF SUPERDISINTEGRANTS [33-34]

Since superdisintegrant is utilized as an excipient in the tablet detailing, it needs to meet certain measures other than its enlarging properties.

1. Poor solvency.
2. Poor gel arrangement.
3. Good hydration limit.
4. Good trim and stream properties.
5. No inclination to frame edifices with the medications.
6. Good mouth feel.
7. It ought to likewise be viable with the other excipients and have attractive tableting properties.

Albeit some are superior to other people, the right now showcased superdisintegrants display an ideal mix of properties.

TYPES OF SUPERDISINTEGRANTS [35-47]

1. Natural superdisintegrants
2. Synthetic superdisintegrants
3. Co-processed superdisintegrants

NATURAL SUPERDISINTEGRANTS [35]

These superdisintegrant-chime specialists are normal in beginning and are liked over engineered substances since they are relatively less expensive, bounteously accessible, non-disturbing and nontoxic in nature. The regular materials like gums and adhesive's have been broadly utilized in the field of medication conveyance for their simple accessibility, cost adequacy, Eco agreeableness, emollient and non-aggravation nature, non-poisonousness, fit for huge number of synthetic adjustments, conceivably degradable and viable because of normal beginning. There are a few gums and adhesive's are accessible which have super-deteriorating movement.

Plantago ovata Seed Mucilage (Isapgula) [35]

Isapghula comprises of dried seeds of the plant Plantago ovata and it contains adhesive which is available in the epidermis of the seeds. The seeds of Plantago ovata were absorbed refined water for 48 hrs and afterward bubbled for few moments for complete arrival of adhesive into water. The material was just barely gotten through muslin fabric for sifting and isolating out the marc. Then, at that point, an equivalent volume of CH3)2CO was added to the filtrate to accelerate the adhesive. The isolated adhesive was dried in stove at temperature under 60°C. The adhesive of Plantago ovata is a new development for its superdisintegration property when contrasted and crosspovidone. It shows quicker deterioration time than the superdisintegrant crosspovidone.

***Lepidium sativum* Mucilage [36]**

Lepidium sativum (family: Cruciferae) is known as asaliyo and is broadly utilized as natural medication in India. It is generally accessible in market and has exceptionally minimal expense. Parts utilized are leaves, root, oil, seeds and so forth Seeds contain higher measure of adhesive, dimeric imidazole alkaloids lepidine B, C, D, E and F and two new monomeric imidazole alkaloids semilepidinoside An and B Mucilage of *Lepidium sativum* has different trademark like restricting, breaking down, gelling.

***Gum karaya* [36]**

Gum karaya is a negative colloid and a perplexing polysaccharide of high atomic weight. On hydrolysis it yields galactose, rhamnose and galacturonic corrosive. Gum Karaya happens as a to some degree acetylated subsidiary. It is a dried exudation of Sterculia Uren tree (FamilySterculiaceae). Its equivalent words are Karaya, sterculia, Indian tragacanth, Bassora tragacanth, kadaya, Kadira, katila. Gum Karaya is viable with other plant hydrocolloids just as proteins and starches.

Fanugreek Seed Mucilage [37]

Trigonella Foenum-graceum, usually known as Fenugreek, is a herbaceous plant of the leguminous family. It has discovered wide applications as a food, a food added substance, and as a customary medication. The leaves and both the ready and unripe seeds of *Trigonella Foenum-graceumare* utilized as vegetables. Fenugreek has been utilized in treating colic tooting, looseness of the bowels, the runs, dyspepsia with loss of hunger, constant hack, dropsy, amplification of liver and spleen, rickets, gout, and diabetes. It is likewise utilized as gastro defensive, antiurolithiatic, diuretic, antidandruff specialist, Anti inflammatory specialist and as cell reinforcement. It likewise is utilized in present natal consideration and on increment lactation in nursing moms. Fenugreek seeds contain a high level of adhesive (a characteristic sticky substance present in the coatings of many seeds). Despite the fact that it doesn't break up in water, adhesive structures a gooey tasteless mass when presented to liquids. other adhesive containing substances, its seeds puff up and become smooth when they are presented to liquids. The subsequent delicate mass isn't consumed by the body, however rather goes through the digestive organs and triggers gastrointestinal muscle constrictions.

***Cassia fistula* Gum [37]**

Seeds of *Cassia fistula* gum got from Cassia fistula tree. Gum got from the seeds of Abha et al. Worldwide Journal of Drug Research and Technology 2015, Vol. 5 (1), 01-12 http://www.ijdrt.com 6 Cassia fistula contains β-(1→4) connected dmannopyranose units with arbitrary dissemination of α (1→6) connected d-galactopyranose units as side chain. Carboxymethylation just as carbamoylethylation of Cassia gum is accounted for to further develop cold water dissolvability, further develop thickness and increment microbial opposition when contrasted with local gum Therefore, an endeavor was made to consolidate calcium or sodium salts of carboxymethylated or carbamoylethylated C. fistula gum as superdisintegrant in the plan advancement of FDT.

Guar Gum [38]

Guar gum is a galactomannan, ordinarily utilized in beauty care products, food items and in drug details. Guar gum is principally comprising of the great sub-atomic weight (roughly 50,000-8,000,000) polysaccharides made out of galactomannans and is gotten from the endosperm of the seed of the guar plant, *Cyamopsis tetragonaloba* (L) Taub (Synonym Cyamopsispsoraloides). It is utilized as thickener, stabilizer and emulsifier, and endorsed in many spaces of the world (for example EU, USA, Japan, and Australia). Its equivalents are Galactosol; guar flour; panther gum; meprogat; meyprodor. It has likewise been examined in the readiness of supported delivery network tablets in the spot of cellulose subordinates, for example, methylcellulose. In drugs, guar gum is utilized in solid dosage structures as a folio and disintegrant, and in oral and skin items as a suspending, thickening, and settling specialist, and furthermore as a controlled-discharge transporter. Guar gum has likewise been analyzed for use in colonic medication conveyance.

***Hibiscus rosa-sinensis* Linn. Adhesive [38]**

Hibiscus rosa-sinensis Linn of the Malvaceae family is otherwise called the shoe-flower plant, China rose, and Chinese hibiscus. The plant is accessible in India in large amounts and its adhesive has been found to go about as a superdisintegrant. The leaves contain carotene (7.34 mg/100 g of new material) dampness, protein, fat, sugar, strands, calcium, and phosphorus. Adhesive of *Hibiscus rosa-sinensis* contains L-rhamnose, D-galactose, D--galactouronic corrosive, and D-glucuronic corrosive.

Grasshopper Bean Gum [39]

Grasshopper bean gum is separated from the endosperm of the seeds of the carob tree *Ceretonia siliqua*, which fills in Mediterranean nations. It is likewise called Carob bean gum. Some other natural polysaccharides are starch and cellulose, which are made of long chains of the sugar glucose. giving it marginally various properties, and permitting the two gums to connect synergistically with the goal that together they make a thicker gel than possibly one alone. It shows as a cover and as a disintegrant property at various focus. Drug use of beetle bean gum in different novel medication conveyance frameworks. Grasshopper bean gum has been broadly utilized in food industry as a thickening and gelling specialist. Grasshopper bean gum has additionally been accounted for to have bioadhesive and dissolvability upgrade properties. There are different reports that Locust bean gum can be utilized in drug and biotechnological reason.

Mango Peel Pectin [39]

Dried mango strip powder is use for extricating gelatin. Maybe mango strip gelatin can't be utilized for promising the conduct of superdisintegrants, yet because of its great expanding file and great solvency in organic liquids it tends to be utilized to plan quick dispersible tablets (Shihora H and Panda S, 2011; Mangal M et al., 2012). Different Natural Superdisintegrant alongside various medications and technique took on for their planning as portrayed in table 5.

SYNTHETIC SUPERDISINTEGRANTS [40]

Synthetic super-disintegrants are regularly utilized in tablet definitions to work on the rate and degree of tablet deterioration in this manner expanding the pace of medication disintegration. The most generally utilized manufactured superdisintegrants are outlined underneath.

Sodium Starch Glycolate (Explotab® and Primogel®) [41]

These are changed starches made by crosslinking of potato starch as it gives the item with the best deteriorating properties. The level of crosslinking and replacement are significant factors in deciding the adequacy of these materials as superdisintegrants. The impact of the crosslinking is to diminish both the water dissolvable part of the polymer and the consistency of scattering in water. The instrument by which this activity happens includes quick assimilation of water prompting a tremendous expansion in volume of granules that outcome in fast and uniform breaking down. These are accessible as explotab and primogel which are low subbed carboxy methyl starches. The impact of presentation of the enormous hydrophilic carboxymethyl bunches is to upset the hydrogen holding inside the polymer structure. This permits water to enter the particle and the polymer becomes cold water solvent.

Cross-Linked Poly-Vinyl Pyrrolidone (Crosspovidone) [41]

Not at all like other superdisintegrants, which depend basically on expanding for deterioration, crosspovidone utilize a mix of enlarging and wicking. Because of its high crosslink thickness, crosspovidone enlarges quickly in water without gelling. Crosspovidone particles are observed to be granular and profoundly permeable which works with wicking of fluid into the tablet and particles to produce fast breaking down. Bigger particles give a quicker crumbling than more modest particles. Crosspovidone disintegrants are exceptionally compressible materials because of their interesting molecule morphology. Crosspovidone can likewise be utilized as solvency enhancer. It is accessible in two molecule sizes as Polyplasdone XL and Polyplasdone XL-10.

Altered Cellulose (Crosscarmellose Sodium, AcDi-Sol) [42]

It is an inside cross connected polymer of carboxymethyl cellulose sodium. It has high expanding limit with insignificant gelling bringing about quick breaking down .Due to sinewy construction, crosscarmellose particles likewise show wicking activity .In tablet definitions, crosscarmellose sodium might be utilized in both direct pressure and wet-granulation measures. At the point when utilized in wet-granulation, the crosscarmellose sodium ought to be added in both the wet and dry phases of the interaction (intra-and extra-granularly) so the wicking and expanding capacity of the disintegrant is best used.

Gums (Ion Exchange Resin) [42]

The INDION 414 and KYRON 314 have been utilized as a superdisintegrant for ODT. It is synthetically cross-connected polyacrylic potassium (Polacrillin potassium), with a utilitarian gathering of – COO – and the standard ionic structure is K+. It has a high water take-up limit. It is a high immaculateness drug grade frail corrosive cation trade tar provided as a dry powder. It is a very successful tablet disintegrant which gives the important hardness and substance strength to the tablet. The item puffs up to an extremely incredible expand when in touch with water or gastrointestinal liquids causing fast breaking down without the development of knots. It is a high atomic weight polymer; thusly it isn't consumed by the human tissues and absolutely alright for human utilization.

L-HPC (Low Substituted Hydroxyl-Propyl Cellulose) [43]

Insoluble in water quickly grows in water. Most prominent level of enlarging displayed by Grades LH-11 and LH-21. Certain grades while holding deterioration limit can likewise give some limiting properties. Suggested fixation 1-5%. The principle benefits of manufactured super disintegrants are their viability in lower fixations than starch, less obstruction with compressibility and stream capacity. They are likewise more compelling intragranularly.Various Synthetic Superdisintegrant alongside various medications and strategy embraced for their readiness as portrayed in table 4.

Advantages of Synthetic Superdisintegrant [44]

- Effective in lower focuses than starch.
- Less impactable on compressibility and stream capacity.
- More viable intragranularly.

Limitions of Synthetic Superdisintegrant [44]

- More hygroscopic (might be an issue with dampness touchy medications).
- Some are anionic and may cause some slight in-vitro restricting with cationic medications (not an issue in-vivo).
- An acidic medium essentially diminishes the fluid take the rate and limit of sodium starch glycolate and crosscarmellose sodium, still not crospovidone.
- The level of expanding of Primojel is limited after wet granulation plan. At last, the medium ionic strength was found to adversely affect the expanding limit of crosscarmellose.

CO-PROCESSED SUPERDISINTEGRANTS [35,45-47]

Better than ever superdisintegrants keep on being created to address the issues of cutting edge tablet fabricating. It requires the advancement of different added usefulness excipients, which are utilized to accomplish definitions with wanted end impacts. As of recently just superdisintegrants are accessible to set up the dose structures, yet presently days distinctive mix of excipients are accessible which can give breaking down property. Some coprocessed excipients mixes are intended to fulfill the need of more than one excipients.

Co-Processed Blends of Excipients [35]

It includes the combination mix of more than two excipients to fulfill the necessary quality utilizing distinctive procedure like splash drying and freeze drying and so on A few models are as per the following:

Ludiflash [45]

Ludiflash is a creative, special co-prepared mix of Mannitol (95%), crosspovidone (5%) and polyvinyl acetic acid derivation (5%) produced in an approved licensed interaction. It deteriorates quickly inside the space of seconds with delicate, smooth consistency. It is uniquely intended for direct pressure on standard high velocity tablet machine for hard tablet with extremely low friability. It gives amazingly quick delivery rate.

F-Melt [45]

F-MELT® is a splash dried excipient utilized in orally breaking down tablets that contain saccharides, deteriorating specialist, and inorganic excipient. F-MELT displays brilliant tableting properties and works with quick water-infiltration for a quick crumbling time.

Pharmaburst [45]

Pharmaburst is a speedy dissolving conveyance framework in which there is expansion of dynamic medication in a dry mix with Pharmaburst excipients and pack by tablet machine. Pharmaburst is a co-prepared excipient framework with explicit excipients, which permits quick crumbling and low attachment to punches.

Altered Chitosan with Silicon Dioxide [46]

This is the new excipients dependent on coprecipitation of Chitosan and silica. The actual collaboration among Chitosan and silica make an insoluble, hydrophilic profoundly permeable material, bringing about prevalence in water take-up, water immersion for gelling development. Studies have shown that Chitosan–silica conveys prevalent execution in wet granulation details and is the just disintegrant that is powerful at all focuses in tablet definition.

Changed Mannitol [46]

Pearlitol 200 SD

These are the granulated Mannitol white, scentless, somewhat sweet tasting, translucent powder. It has a special mix of outstanding physical and compound dependability, with incredible organoleptic, non-cancer-causing, without sugar properties. Along with its flexible powder properties, it very well may be utilized in various cycles wet or dry granulation, direct pressure and compaction or freeze-drying. It has properties like flowability, astounding compressibility, nonhygroscopic and incredible synthetic solidness. Pearlitol SD breaks up quickly due to its permeable translucent particles.

Mannogem EZ [46]

Mannogem EZ is splashing dried Mannitol, extraordinarily intended for direct pressure tablet. It enjoys benefits of profoundly viable, non hygroscopic, artificially inactive, restricted molecule size appropriation and primarily fast deterioration property helps speedy disintegrate application. It is exceptionally steady and dormant to large numbers of the synthetic responses which are dangerous with lactose, microcrystalline cellulose, or starch.

Changed Resins Polacrilin Potassium (Tulsion 339) [47]

It is a crosslinked polymer of methacrylic corrosive and divinylbenzene provided as the potassium salt. Polacrilin potassium is feebly acidic cation trade tar. On wetting, the gum enlarges by roughly 150 %, in this way making the tablet deteriorate. Tablet breaking down property is because of its amazingly enormous expanding limit in watery arrangements. Water can apply power between particles inside tablet pores, however this power is low. This is utilized successfully at 1-2% of strong dose structures. It is bio viable and non-poisonous. It is accessible in different grades i.e., tulsion-335, tulsion-344, tulsion-345 and tulsion-412.

Changed Sugars Glucidex IT [47]

Glucidex IT is gotten by moderate hydrolysis of starch. It is miniature granulated structure empowers practically momentary dispersal and disintegration in water. Distinctive scope of Glucidex IT items is accessible. All co-prepared and adjusted excipients are assuming an imperative part in the advancement of simple measurement

structures which are impervious to climate. The worked on physical, compound and mechanical properties of such excipients when contrasted with existing excipients have helped in tackling plan issues like flowability, compressibility, hygroscopicity, agreeability, disintegration, breaking down, staying, and dust generation.Various Multifunctional Superdisintegrants as displayed in predicts the information of various superdisintegrant utilized and their number of licenses. It is a joined information gotten from NIC and USPTO data set. From the table it tends to be seen that Amylose is the most generally licensed superdisintegrants.

DISINTEGRANTS IN DISPERSIBLE TABLETS [48]

Disintegrants are specialists added to tablet details to advance the separation of the tablet into more modest sections in a watery climate, accordingly expanding the accessible surface region and advancing a more quick arrival of the medication substance. In later years, a few fresher disintegrants have been grown, regularly called "super disintegrants". These fresher substance can be utilized at lower levels than ordinarily utilized disintegrants. Three significant components and elements influencing tablets disintegrants are proposed as expanding, porosity and narrow activity and twisting. Three significant gathering of compound that have been created as superdisintegrants are adjusted starches, cross-connected polyvinylpyrrolidone and altered cellulose.

TECHNIQUES FOR FORMULATION OF ORALLY DISINTEGRATING TABLETS [49-53]

1. Freeze drying / Lyophilization
2. Tablet Moulding
3. Spray drying
4. Sublimation
5. Direct compression
6. Mass extrusion

FREEZE DRYING [49]

Freeze drying is the cycle wherein water is sublimed from the item after it is frozen. This strategy makes a nebulous permeable construction that can disintegrate quickly. A common method associated with the assembling of ODTS utilizing this procedure is referenced here. The dynamic medication is broken down or scattered in a watery arrangement of a transporter/polymer. The combination is poured in the dividers of the performed rankle packs. Then, at that point the frozen rankle packs are set in refrigerated cupboards to proceed with the freeze-drying. After freeze-drying the aluminum foil backing is applied on a rankle fixing machine. At last the rankles are pressed and delivered. The freeze-drying method has exhibited further developed retention and expansion in bioavailability. The significant impediments of lyophillization procedure are that it is costly and tedious; delicacy makes traditional bundling unacceptable for these items and helpless dependability under focused on conditions.

TABLET MOULDING [50]

Embellishment measure is of two sorts (dissolvable strategy and warmth technique). Dissolvable strategy includes dampening the powder mix with a hydro alcoholic dissolvable followed by pressure at low pressing factors in shaped plates to frame a wetted mass (pressure forming). The dissolvable is then eliminated via air-drying. The tablets made thusly are less smaller than packed tablets and have a permeable construction that rushes disintegration. The warmth forming measure includes readiness of a suspension that contains a medication, agar and sugar (for example mannitol or lactose) and pouring the suspension in the rankle bundling wells, hardening the agar at the room temperature to frame a jam and drying at 30○C under vacuum. The mechanical strength of shaped tablets involves incredible concern. Folios, which increment the mechanical strength of the tablets, should be fused. Taste covering is an additional issue to this innovation. The taste covered medication particles were ready by shower solidifying a liquid combination of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and a functioning fixing into a lactose based tablet pulverize structure. Contrasted with the lyophillization procedure, tablets delivered by the trim strategy are simpler to increase for modern production.

SPRAY DRYING [51]

In this procedure, gelatin can be utilized as a supporting specialist and as a grid, mannitol as a building specialist and sodium starch glycolate or croscarmellose or crospovidone are utilized as superdisintegrants. Tablets made from the spraydried powder have been accounted for to deteriorate in under 20 seconds in watery medium. The plan might contain building specialist like mannitol and lactose, a superdisintegrant like sodium starch glycolate (or) croscarmellose sodium, acidic fixing (citrus extract) and basic fixing (for example sodiumbicarbonate). This spraydried powder, when compacted into tablets might create fast breaking down and disintegration.

SUBLIMATION [51]

In this technique to produce a permeable network, unstable fixings are fused in the detailing that is subsequently exposed to a course of sublimation. ammonium bicarbonate, ammonium carbonate, benzoic corrosive, camphor, naphthalene, urea, urethane and phthalic anhydride might be compacted alongside other excipients into a tablet. This unpredictable material is then eliminated by sublimation leaving behind an exceptionally permeable grid. Tablets made by this strategy have answered to generally break down in 10-20 sec.

DIRECT COMPRESSION [52]

Direct pressure addresses the easiest and most practical tablet fabricating procedure. This procedure can be applied to readiness of ODTS on account of the accessibility of improved excipients particularly superdisintegrants and sugar based excipients.

(a)Super Disintegrants: [52]

In many orally deteriorating tablets advancements dependent on direct pressure, the expansion of superdisintegrants increment the pace of crumbling and thus the disintegration. The presence of other definition fixings, for example, watersoluble excipients and bubbly specialists further rushes the course of crumbling.

(b)Sugar Based Excipients: [52]

This is one more way to deal with make ODTS by direct pressure strategy. The utilization of sugar based excipients particularly building specialists like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol will show high watery solvency and pleasantness and thus bestow taste covering property and a satisfying mouth feel. Mizumito et al have arranged sugarbased excipients into 2 kinds based on embellishment and disintegration rate.

Type 1 Saccharides (lactose and mannitol) display low shape capacity yet high disintegration rate.

Type 2 Saccharides (maltose and maltilol) display high form capacity and low disintegration rate.

MASS EXTRUSION [53]

This innovation includes mellowing the dynamic mix utilizing the dissolvable combination of water-solvent polyethylene glycol and methanol and ensuing ejection of relaxed mass through the extruder or needle to get a chamber of the item into even fragments and utilizing warmed edge to frame tablet. The dried chamber can likewise be utilized to cover granules for harsh medications and in this way accomplish taste veiling.

PATENT TECHNOLOGIES FOR ORALLY DISINTEGRATING TABLETS [54-55]

1. Zydis Technology
2. Durasolv Technology
3. Orasolv Technology
4. Wow tab Technology
5. Flash Dose Technology
6. FlashTab Technology
7. Oraquick Technology
8. Nanocrystal Technology

Zydis Technology [54]
It was protected by Zydis. In this innovation, the medication is entangled inside the network of quick dissolving transporter. The item is a novel freeze dried tablet that breaks down on tongue inside 2-3 sec.

Durasolv Technology [54]
It was licensed by CIMA Labs. In this innovation, drug is blended in with fillers and oil and tablets product arranged utilizing customary tableting machines.

Orasolv Technology [54]
It was likewise licensed by CIMA Labs. This innovation produces tablets including taste veiled medicaments and bubbly breaking down specialists arranged by direct pressure technique.

Wow Tab Technology [54]
It was licensed by Yamanouchi Pharmaceutical Co. WOW alludes to With out Water. This innovation uses mixes of low and high mouldability saccharides to get quickly dissolving tablets.

Streak Dose Technology [55]
It was protected by Fuisz. This innovation produces tablets comprising of selfbinding shear structure lattice called as "floss" ready by streak warming cycle.

FlashTab Technology [55]
It was licensed by Prographarm research facilities. In this innovation, dynamic fixings are made into microgranules utilizing strategies like coacervation or microencapsulation and tableted utilizing customary innovation.

Oraquick Technology [55]
It was protected by KV Pharmaceuticals. In this innovation, drug is microencapsulated and encircled by a lattice making it more flexible.

Nanocrystal Technology [55]
Pace of disintegration can be expanded by diminishing the molecule size. In this innovation, drugs are processed to little particles

STAGES OF DISINTEGRATION
The different stages of disintegration of ODTS were shown in Fig:3

FACTOR AFFECTING ACTION OF DISINTEGRANTS [56-57]
- Percentage of disintegrants present in the tablets.
- Types of substances present in the tablets.
- Combination of disintegrants.
- Presence of surfactants.
- Hardness of the tablets.
- Nature of Drug substances.
- Mixing and Screening.

CHOOSING AN OPTIMAL SUPERDISINTEGRANT [58]
Consider the effect of the superdisintegrant concerning the exhibition of the last dose structure. As medication disintegration is fundamental for assimilation by the body, formulators at this point not select disintegrants dependent on the most minimal deterioration time since additionally consider the impact of the superdsintegrant on disintegration. Moreover, the ionic idea of both the API and the superdisintegrants should likewise be thought of.

Anionic superdisintegrants, for example, croscarmellose sodium and sodium starch glycolate, can connect with cationic APIs and retard disintegration. In this manner, nonionic superdistegrants are favored when working with cationic APIs. Formulators additionally consider the effect of the superdisintegrant on actual tablet qualities, for example, tablet breaking power and friability. In the present high velocity tablet presses, superdisintegrants that give tablets high breaking power and low friability, while keeping up with quick deterioration, are especially significant.

APPICATIONS OF SUPERDISINTEGRANTS [59]

The employments of superdisintegrants are stretched out in the utilizations of oral breaking down tablets, quick dispersible tablets, cases, mouth-dissolving films, and so forth Especially for ODTs and quick dispersible tablets, are improved dependent on their crumbling time. ODTs should be deteriorated within the sight of spit in oral pit inside a moment. Consequently these details accomplish better understanding consistence in all classes from pediatric to geriatric, laid up and uncooperative patients including regular explorers as it requires practically no entrance of water.

The approach of superdisintegrants in different details

The approch of superdisintegrants in different details, the developments, currently protected in related field are recorded as

Pharmaceutical superdisintegrant (US20050100600):

Superdi/sintegrants which give further developed compressibility contrasted with earlier craftsmanship superdisintegrants. The superdisintegrants incorporate a particulate agglomerate of coprocessed starch or cellulose and an adequate measure of an enlarging specialist to expand the compactibility of the superdisintegrant.

Rapidly deteriorating protein containing strong oral dose sytheses (US20060013807):

Development identifies with quickly breaking down strong oral dose structures having a compelling measure of a protein and a superdisintegrant. The protein lactase is guaranteed in this patent for strong oral plans.

Fast deteriorating tablets (US20050169986)

A quick deteriorating tablet including Nimesulide and at least one disintegrants. In this exploration superdisintegrants utilized are croscarmellose cellulose, crospovidone and sodium starch glycolate.

Method of creating quick dissolving tablets (US20100074948)

A strategy for delivering a quick liquefy tablet. The cycle doesn't include any granulation step, subsequently making the interaction more energy productive and practical. The quick dissolving sugar liquor is chosen from the gathering including: mannitol; sorbitol; erythritol; xylitol; lactose; dextrose; and sucrose. The dynamic part is reasonably given as microparticles or microcapsules having a normal measurement of under 125 microns.

Disintegrating Loadable Tablets (US20090186081)

A deteriorating loadable tablet item in packed structure. A disintegrant or a combination of disintegrants has a) porosity of 45% v/v or more, b) a hardness of no less than 20 Newton, and c) a stacking limit of essentially 30% of a fluid.

Rapidly deteriorating tablet (US20060115528)

The review identifies with quickly deteriorating tablets expected to be utilized as orodispersible tablets or dispersible tablets. The tablets incorporate silicified microsrystalline cellulose. They are particularly reasonable for anti-infection agents. Quickly crumbling tablets which contain amoxicillin and clavulanic corrosive are likewise portrayed.

CONCLUSION

In original medication conveyance, the quick dissolving drug conveyance framework has become one of the achievement of present examination. The developments in the field of defining ODTs are focused on both expanding the exhibition of the measurement structure by diminishing the crumbling time. Disintegrants are substances or combination of substances added the medication definition that works with the separation or deterioration of tablet or case content into more modest particles that break down more quickly than without a trace of disintegrants. Superdisintegrants are for the most part utilized at a low level in the strong measurement structure, ordinarily 1-10 % by weight comparative with the absolute weight of the dose unit. The current review involves the different sorts of superdisintegrants which are being utilized in the plan to give the more secure, viable medication conveyance with patient's consistence. Likewise, extensive examination towards creating altered microcrystalline cellulose or starch to design them reasonable for direct pressure has altogether decreased the item improvement time for streamlining ODT definition. Quickly breaking down dose structures have been effectively marketed by utilizing different sorts of superdisintegrants.

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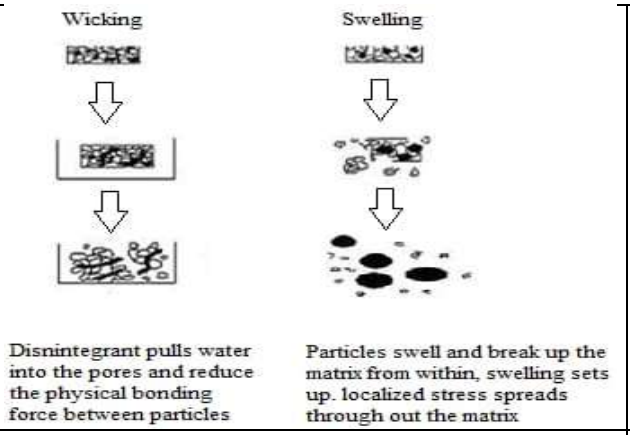

Figure. 1. wicking and swelling mechanism

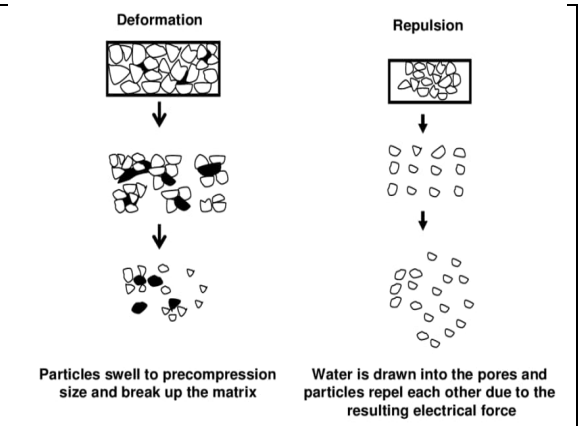

Figure. 2. deformation and repulsion mechanism

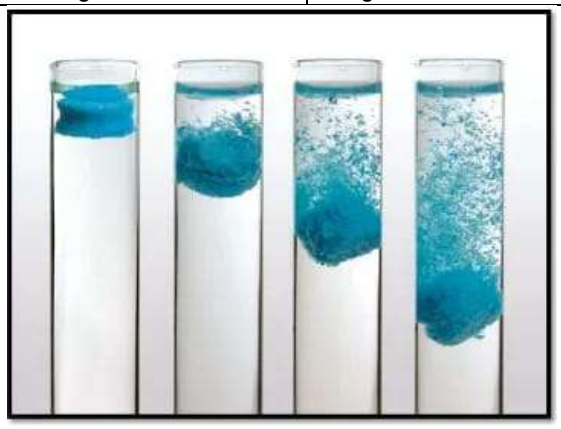

Figure. 3 .The different stages of disintegration of ODTS

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RESEARCH ARTICLE

Prevalence of Primary Dysmenorrhea among Adolescent Girls in Rajasthan Sirohi District- A Cross Sectional Study

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ABSTRACT

Primary dysmenorrhea may be a painful menstrual cramp of uterine origin. It is the main common gynaecologic problem in adolescence girls and young women. The significant symptoms including pain, educational attainment and adverse effect on lifestyle, causing recurrent short-term school absenteeism among adolescent girls. Accordingly, the current study focused to estimate the prevalence of primary dysmenorrhea among adolescent girls age between (14-19yrs) in sirohi district, Rajasthan. This was a cross sectional study conducted from oct 2019 to February 2019 among 672 Adolescent girls in government Schools Rajasthan using a MOOS menstrual distress questionnaire. In this study, severity of primary dysmenorrhea was significantly high. There was association between menstrual pain and limited activities. Primary dysmenorrhea may be a quite common problem among adolescent girls and it affects their quality of life. It will be better managed by mental preparation and by appropriate change in lifestyle like regular exercise.

Keywords : Adolescent girls, primary dysmenorrhea, sickness absenteeism, quality of life.

INTRODUCTION

Menstruation could be a phenomenon among matured females, experiencing shedding of blood for 1-7 days each month from the age of maturity (10 to 12 years of age) until menopause (45 to 50 years of age) [3]. Every woman, on a mean, experiences menstruation which may be a mark of her reproductive potential. Some women, before or during menstruation also had to alter dysmenorrhea which could be a painful cramping sensation within the lower

abdomen and sometimes in the middle of headache, dizziness, diarrhoea, bloated feeling, nausea and vomiting, backache and leg pains. Major symptoms, including pain, adversely affect standard of living and faculty performance, causing recurrent short-term school absenteeism among female adolescents [4,5,6,7,8]. Primary dysmenorrhoea refers to the painful menstruation. But to be more precise it means menstruation with heavy pain specified it interferes with daily activities. In oscillation the uterine walls thicken to arrange for the upcoming pregnancy [11,13,14]. Adolescence means 'to emerge' to attain 'identity'[17]. Personhood is what we would like the Adolescent to achieve not barely in its physical or intellectual aspects but also in his/her whole humanhood, which has the usually neglected but equally important aspects, which are social, spiritual and emotional or psychological [1,2]. This study aimed toward estimating the prevalence of dysmenorrhea among adolescent girls in Rajasthan sirohi district.

MATERIALS AND METHODS

This was a cross sectional study conducted in schools present in sirohi district, Rajasthan. Final year physiotherapy students and interns were trained for this study. Eight schools randomly selected and from this all the Adolescent girls age group between 13-16 years, who attained menarche, girls with premenstrual symptoms and Pelvic pain, girls who are willing to participate with their parents' permission, girls who had regular cycle between 21 to 40 days for the past three cycles, girls with BMI ≥ 18.5 and with Oligo / amenorrhea were included in the study. Adolescent Females who are under treatment for any uterine problem, who are physically challenged, who are taking any pain killer or spasmodic drug regularly for any other problem, who were already practicing yoga, those who are having any other gynaecological problem, who underwent any minor or major surgery within 3months and who were absent on the day of data collection was excluded.

All the participants were interviewed with the help of MOOS menstrual distress questionnaire consisting of most recent menstrual flow, the week preceding the menstrual flow and the remainder of menstrual cycle. The study was performed on total of 672 students who agreed to participate in the research. All 672 students surveyed at school completed the questionnaire. Out of 672 participants 402 students were reported primary dysmenorrhea. A list of 47 symptoms for inclusion in the menstrual distress questionnaire was obtained from several Sources To detect the prevalence and severity of the premenstrual syndrome. (27- 34). All the components in the questionnaire were first described by the researcher supervising the study in local language. Then they were asked to respond for the given questionnaire. Each subject was interviewed with the open-end questionnaire which elicited information about many possible menstrual cycle symptoms. The informed consent was taken from them and were told that their information would be kept confidential. The questions related to menstruation were age of menarche, marital status, parity, regularity of the cycles, length of cycle, and duration of menstrual flow. A background additive and supportive information was obtained about their education, religion, home town, height, weight, socio-economic status, occupation of the parents, total family members, dietary habits, habits of regular physical exercise and family history of dysmenorrhoea. The study included adolescent girls of government schools of sirohi district Rajasthan. A set of questions were used to evaluate the menstrual symptomatology, which consisted of 47 symptoms under 8 different headings. These factors under each heading, even though represent separate were empirically inter related clusters of symptoms. The questionnaire method is selected because, it elicits a concrete data about own subjective assessment of the extent of her disability, which is a most reliable and important essential source of information. Large population of women can be assessed to estimate the prevalence and severity of different types of menstrual symptoms. Also, it is possible that these types of specific analyses may identify new subtypes or groups of symptoms which may show specialized relationships either to psychological, neural or endocrinal factors.

All the students body mass index (BMI) were measured by Weight (Kg)/ Height^2 (meter)^2. Asian principles for BMI have been taken in analysis. <18, 18-22.99 and >23 was taken as cut off for underweight, normal and overweight.

RESULTS

Total 672 female adolescents completed the questionnaire. The prevalence of primary dysmenorrhea was 60%. Among participants reporting primary dysmenorrhea every month is 29.35%, most of the months is 22.13%, occasionally 17.16% and rarely 31.34%. among participants, 46% adolescent girls indicated that primary dysmenorrhea limited their activities due to irritability, 71% reported backache, 94% reported cramps, 29% reported with confusion, 82% reported insomnia, 83% reported depression, 80% reported painful breast, 48% reported tension, 77% reported avoiding social activities and 90% reported headache. The school absenteeism was 76.3% among participants reporting dizziness and 76% reporting taking naps during primary dysmenorrhea.

DISCUSSION

Primary dysmenorrhea may be a common health issue among adolescent women. Being conscious of the factors that are related to its intensity makes it possible for health professionals to arrange better programmes to scale back the adverse effects of primary dysmenorrhea. The prevalence of dysmenorrhea was 89.1% (nahal Habibi 2014), (nazarpour 2010), (omidvar and begum 2012), (Ortiz 2010). zhou and yang (2010), a prospective study conducted on 23,640 chinese adolescent girl students reported that the severity of menstrual pain was related to greater amount of menstruation. In the present study of 672 female subjects aged between 13 to 16 years, mean age of menarche in this study was 13 years in students having primary dysmenorrhea. Homogeneous outcomes were observed in the research study conducted by Gulsen Eryilmaz et al, Demr SC et al; Vicdan K et al in Turkey.

Results of this study showed that higher intensity of dysmenorrhea was related to younger ages, and a few previous studies confirmed that the intensity of dysmenorrhea decreased as age increased (Juang et al., 2006). In this study, severity of dysmenorrhea was significantly high. There was association between menstrual pain and limited activities. Many research studies explained that the prevalence of primary dysmenorrhea exhibited that there is decrease with increasing of their age, indicating that primary dysmenorrhea peaks in late adolescence and also the early 20s and also the prevalence falls with increasing age [20,22,23,24]. However, this study failed to find any connection between age groups and also the prevalence of primary dysmenorrhea. This is often probably because the scholars might not be in a very higher range of years. In a research study surveyed by Gulsen Eryilmaz et al had found out that incidence of vomiting and nausea, diarrhoea, giddiness and headache was 12.2%, 8.1%, 8.1% and 17.7% respectively among the adolescent girl students of 26 high schools located in Erzurum, North-eastern Turkey11.

CONCLUSION

To conclude, this study confirmed that primary dysmenorrhoea may be a quite common problem among adolescent girls, and that they experience variety of physical and emotional symptoms related to primary dysmenorrhea and it also affects their quality of life. It may be better managed by mental preparation and by appropriate change in lifestyle like regular exercise. Girls should be reassured that their problem is probably going to be short lived and may be managed by some self-help techniques, indulging in work instead of seeking drugs.

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Table 1. Frequencies and percentage of adolescent girls experiencing primary dysmenorrhea

Sl. No	Adolescent girls with primary dysmenorrhea states	Frequency (402)	percentage
1.	Primary Dysmenorrhea Every month	118	29.35
2.	Most of the months	89	22.13
3.	Occasionally	69	17.16
4.	Rarely	126	31.34

Table 2 Percentage of ten commonly occurring associated symptoms of menstruation and primary dysmenorrhea Among adolescent Girls.

Sl. No	Symptoms	Most recent flow	Week before	Remainder of the cycle
1.	Irritability	120	56	12
2.	Backache	153	71	60
3.	Cramps	193	101	84
4.	Confusion	72	24	20
5.	Insomnia	187	94	49
6.	Depression	91	183	60
7.	Painful breasts	212	118	72
8.	Tension	95	50	51
9.	Avoid social activities	67	169	77
10.	Headache	191	103	69

Table 3 Association between menstrual pain and limited activities

Sl.No	Symptoms	Mild	Moderate	Severe
1.	Stay at home	145	122	40
2.	Dizziness	60	42	50
3.	Nausea/ vomiting	75	51	64
4.	Take naps/ stay in bed	71	149	86
5.	Diarrhea	82	67	30
6.	Difficulty in concentration	95	110	159

Table 4 Relationship between primary dysmenorrhea and BMI

BMI	Primary Dysmenorrhea Present (402)	Absent (270)
<18.5	132	79
18.5 - 24.9	210	140
25- 29.9	60	51

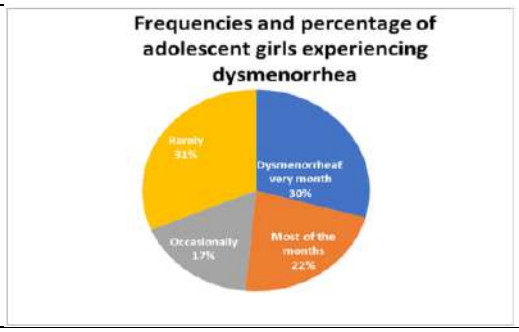

Figure 1 showing the Frequencies and percentage of adolescent girls experiencing primary dysmenorrhea

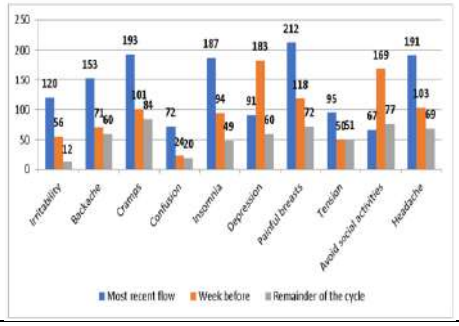

Figure 2 Associated symptoms of menstruation and primary dysmenorrhea Among adolescent Girls.

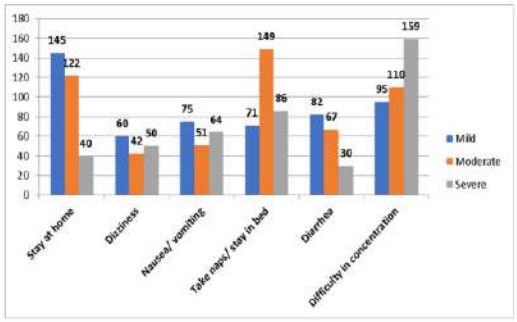

Figure 3 symptoms Associated between menstrual pain and limited activities

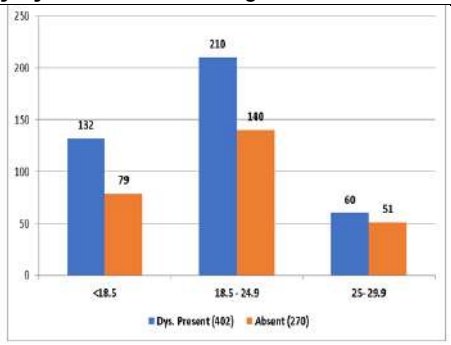

Figure 4 Relationship between primary dysmenorrhea and BMI

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REVIEW ARTICLE

A Review on Medicinal Importance of Guggulsterone in Guggul (*Commiphora wighti)*

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ABSTRACT

Guggulsterone is a plant sterol obtained from gum resin of Guggul. To treat various disorders, including internal tumors, obesity, liver disorders, malignant sores and ulcers, urinary complaints, intestinal worms, leucoderma, sinuses, edema, and sudden paralytic seizures the gum resin which is obtained from Guggul plant used for thousand years in ayurveda. Guggulsterone has been identified a bioactive components of this gum resin. For the regulation of bile acids and cholesterol metabolism it works as antagonist of nuclear receptors such as farnesoid X receptor. It also inhibits the cancers cells by activating p38 pathway, protein kinase and nuclear kappa cells for causing apoptosis which results in cell proliferation. Gugggulsterone eradicated cholesterol metabolites bile acids from the liver by upregualting bile salt export pump and also proposed a system of anti-inflammatory effect by repression of NF-κB activation. Gugglesterone activates 3T3L1 adipocytes which leads to mitochondrial biogenesis which leads to weight loss. This review paper reveals the importance of Guggul due to its medicinal value which aimed to clarify the role of Gugglesterones in chronic diseases and its mode of action which helps in the future research studies.

Keywords: cancer, antiinflamtory, hyperlipidemia, weight loss.

INTRODUCTION

From the past few decades the world has substantially seen an exponential increase in population rise, inadequate supply of drugs, prohibitive cost of treatments, side effects of several synthetic drugs and the economic forum has

always stated that the resources on earth are limited, an optimum use of available technology and new modificants will enhance the productivity to three folds and this has popularised the use of plant materials in sectors of medicines and agriculture for wide variety of human ailments.(Soni and Swarnkal 2006).

Due to its rare or minimal side effect treating with medicinal plant contemplates very safe and important fact arises that herbal treatments is independent of any age groups. Guggul *(Commiphora wightii*) comes under the critically endangered species and considered as important medicinal plant.(Tomar et al.,2021) It is mostly found in Bangladesh ,Pakistan, Rajasthan, Gujarat, Assam, Madhya Pradesh, and (Kulloli and Kumar, 2013).Guggulis having complicated mixture of minerals, gum, terpenes, sterols (Guggulsterol -I,-II,-III,-IV,-V), essential oils, sterones (Z-, E-, M-Guggulsterone, and dehydro Guggulsterone-M), ferrulates, lignans, and flavanones.(Shishodia et al., 2008).One of the main sterol of Guggul is Guggulsterone. It plays a vital role which controls the synthesis and transport of bile acidby suppressing the physiological action of the nuclear hormone receptor i.e FXR (Sinal and Gonzalez, 2002; Urizar et al., 2002).It also has been reported that it found for exerting theanti-metastic effect by reducing the level of MMP-9, COX-2, and VEGF (Shishodia and Aggarwal, 2004). It also modulates the expression of anti-apoptotic genes for inducing apoptosis (Shishodia and Agarwal, 2004).

This review paper summarizes the medicinal importance of Gugglesterone for treatment of human health such as followingtreating inflammatory conditions, diabetes, weight loss, hypothyroidism, cancer, hyperlipidemia and also has the future possibilities for obtaining herbal medicines for the health benefits of the people.

For treatment of hyperlipidemia

Guggul considered the important medicinal plant due to its various medicinal properties.In asia Guggul have been widely used for cholesterol-lowering agents and their popularity is increasing in the United States. Guggulsterones -E and -Z are responsible for the lipidlowering properties of Guggul in human blood. To evaluate the effects of Guggulsterone on disorders of lipid metabolism,studies are finding out. The study of Singh *et al*. (2007) reveals that Guggulsterone (25 mg/kg body weight for 10 days) lowered serum cholesterol and triglyceride levels by 27% and 30%, respectively. Chander *et al* (2002) examine the effect of Guggulsterone decreased serum levels of LDL and very low-density lipoprotein. To understand the role of Guggulsterone for the treatment of hyperlipidemia the following pathway Fig. 1.

As we all can see in fig.1 that Guggulesterone activates FXR receptor factor which is metabolism regulator found in liver and intestine which regulates protein coding gene i.e CyP7α1 which modulates the enzyme 7α hydrolase for synthesis of bile acid from cholesterol and also upregulate the bile salt export pump.FXR receptor also activates bile acid binding protein gene 1-BABP for cholesterol homeostasis which treated with αPPAR leads to uptake of bile salt. (Urizar et al.,2002; Chaudhary 2012;Satyavati et al.,1969)

For the treatment of Cancer

For modern drug development Identification of active principles and their molecular targets from traditional medicine is carried out. Gum resin from Commiphora wightii (syn C. mukul) has been used for centuries in Ayurveda to treat internal tumors .Guggulsterone has been identified as one of the major active components of this gum resin. Evidence has been presented through findings to suggest that Guggulsterone can suppress tumor initiation, promotion and metastasis.Crasto (2012)arecent study revealedthat gugulipid which is extracted from *Commiphora mukul*, and mostly used in lowering the cholesterol level effect.Studies also revealed that Guggulsterone recently act as inhibitor for cancer growth invivo and invitro condition and also through the understanding of anti-cancer activity leads to treat different types of human cancer. Shishodia (2007).Guggulsterone suppressed proliferation of tumor cells through inhibition of DNA synthesis, producing cell cycle arrest in the S phase. Silva et al (2014) while investigating the role of bone lipids in breast cancer migration to bone showed that the FXR antagonist Z-Guggulsterone prevented migration of these cells and induced apoptosis in breast cancer cells.To understand the role of Gugglesterone for the treatment of cancer the following pathway is Fig.2. As we can see in fig .2 that

Guggulesterone plays a role for inhibition of cancer cells by activating MAPK pathway which is mitogen activated protein kinase which produce pro apoptotic genes and causes apoptosis .it activates protein kinaseB and NF-Kb pathway which is nuclear factor kappa light chain enhancer of activated b cells.Both MAPK and protein kinase produce cytochrome c and which activate caspase activation and causes cell proliferation. Nf-Kb pathways also produce anti apoptotic genes results in cell proliferation. (Miller et al., 2019; Shishodia 2008; Murthy et al., 2021).

For the treatment of inflammatory conditions

For the treatment of inflammatory conditions Gugglesterone played a vital role by exerting its anti-inflammatory effects through suppression of cytokines. To better understand the role of Guggulsterone on cytokineinduced inflammation, Lv et al. (2015) studied the effect of Guggulsterone on IL-1β- and IFN-γ-induced beta-cell damage in the islets of Langerhans.Denget al, (2007) reported that gugggulsterone eradicated cholesterol metabolites bile acids from the liver by upregualting bile salt export pump.and also proposed a system of antiinflamatory effect by repression of NF-κB activation by Guggulsterone.Neuder LE et.al (2009) examinesGugglesterone induce LPS-stimulated macrophageand manipulate the expression of proinflammatory cytokines and suppress the mrna expressions of IL-1β, TNF-α, and iNOS.

For the treatment of Weight loss

Guggulhad been used as a weight loss aid in Ayurvedic medicine and in 2008 lab study found that the active ingredient in Guggul preparations did cause fat cells to break down. Some studies support the claim that Guggul can be beneficial for weight loss.Urizar et.al (2019) *study* reveals that taking Guggulsterone phosphate supplement alongside regular exercise led to a significant reduction in fat mass.Miller and Samuels, (2019),studied the understanding of anti-obesity effects of Gugglesterone and direct and indirect stimulation of M2 macrophage polarization. And establish the potential anti-obesity effects of Gugglesterone.To understand the role of Gugglesterone for the treatment of weight loss the following pathway is fig.3.

As we can see in fig .3 that Gugglesterone activates 3T3L1 adipocites which leads to mitochondrial biogenesis in which cells increase mitochondrial numbers and it regulates the upregulation of UCP1 for ATP synthesis and reuptake of catecholamine leads to weight loss(Miller et al.,2019;Sethi 2011)

CONCLUSION

For treating chronic diseases such as hyperlipidemia, obesity and also inhibit cancer cells as well as in improving the immune system Gugglesterone played a vital role.Due to minute immunomodulatory effect of Gugglesteronefurther research is required obtaining herbal medicinesfor the health benefits of the people.

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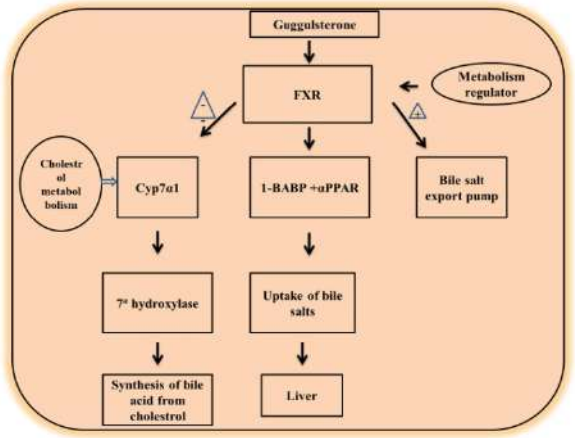

Fig.1. Guggulsterone treating hyperlipidemia

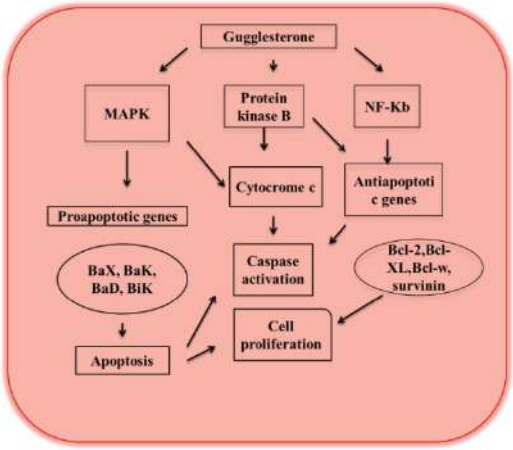

Fig .2. Guggleserone for treating cancer

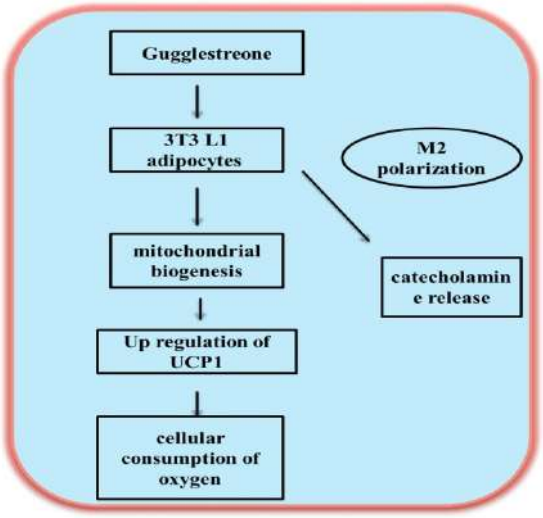

Fig .3. Anti-obesity

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RESEARCH ARTICLE

Nutritional Status, and Quality of Life of HIV Children of Care Givers Living in Residing Home

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ABSTRACT

HIV/AIDS are the most series health problem in the world, the number of people infected with the HIV/AIDS has been increasing all over the world. The study design was descriptive design with quantitative approach, the sample used in this study is convenient sampling technique with 100 . HIV children selected from the care home from Salam order to measure the , nutritional status and quality of life regarding HIV children a semi structured questionnaire with face to face interview of participants has been conducted . Data was analyses by using the statistical software named spss 2.1 According to the finding of this study find out the degree of malnutrition 70% most of the HIV children were in grade 2.and in quality of life 73.3% majority of the HIV children were in sometimes and often by using pedsQL scale.

Keywords: Nutritional status , quality of life , HIV children.

INTRODUCTION

In 2015, 1.8 million children were living with HIV and 150,000 were newly infected with the disease worldwide. Even with the continued scale-up of preventive services, it is estimated that 2 million children will need antiretroviral treatment (ART) in 2021. In 2015, 1.8 million children were living with HIV and 150,000 were newly infected with the disease worldwide. Even with the continued scale-up of preventive services, it is estimated that 2 million children will need antiretroviral treatment (ART) in 2021. Acquired immunodeficiency syndrome (AIDS) is a

chronic, potentially life-threatening condition caused by the human immunodeficiency virus (HIV) that targets the immune system and weakens people's defense against many infections. It is also one of the world's most serious public health challenges, as since it was first identified in 1984, the world has not been able to come up with a possible effective vaccine for it. HIV continuous to be a major global public health issue ,having claimed almost 33 million lives so far However with increasing access to effective HIV prevention , ,treatment & care including for opportunistic infections , HIV infections has become a manageable chronic health condition , enabling people living with HIV to lead long and healthy lives. HIV infection and malnutrition of the co-exist in children and malnutrition is a major problem for HIV- infected children .The risk of malnutrition was significantly higher in HIV- infected children than in HIV- uninfected children . Malnutrition also increased the frequency and severity of infection and delayed recovery from disease.

When compared with HIV-negative children HIV-infected children including asymptomatic children] have additional nutritional requirements to ensure normal growth and development and require high- energy , high protein , nutrient-dense diets calorie intake needs to be increased, with children requiring up to 150% of the recommended daily allowance of calories and micronutrient requirement is up to five time of an HIV- negative child. These increased nutritional demands reflect the increased nutrient cost of immune system support and prevention of muscle wasting.

Recognition of the importance of nutritional considerations in the care of children with HIV lead to the development of guidelines for an integrated approach to the nutritional care of the HIV- infected children. Health related quality of life distinguishes itself from more general quality of life measures in that its preview is limited to factors related to health or health are the reviews are often confined to studies of cognitive performance and do not relate or link these to other developmental measures such as physical development, behaviour or mental health such as depression, anxiety or trauma or positive mental health such as quantity of life exercise program can be effective in improving the health outcomes of patients with HIV undergoing ART to improve body composition and cardiovascular fitness , reduce the risk of diabetes and hyperlipidemia ,there by decreasing CVD risk. The present study was carried out with the objective of assessing the health status, Nutritional status and Quality of life of HIV children of care givers living in residing home in Salem.

METHODS

This descriptive study was conducted among 100 children by AIDS residing in care home giving institution for HIV positive children in Salem .The care giving center provide multitude of services which include basic services like Food, clothing and shelter medical services like treatment for opportunities infections. ART counseling. The institutions were approached and gave approval to conduct the study. Clearance was obtained from institutional ethics committee of vinayaka missions kirupananda variyar medical college of Salem. to conduct the study all the children residing in these institutions during the study period were included. The study was conducted over a period of 1 months. Children were interviewed after obtained informed concerned from the director of the institution interview was conducted by using demographic profile ,pedsQL by semi structure question consist of questionnaire interview was conducted on separate room and took around 30 minutes for each interview . Degree of malnutrition was calculated by using IAP classification and health status assessed by physical examination and quality of life assessed using pediatric quality of life inventory scale for children between 10 to 17 years of boys.

MATERIAL AND ANALYSIS

DATA ANALYSIS

The data were entered in and analyzed using SPSS version 11.5. The results are expressed in mean (standard deviation) and proportions. Degree of malnutrition was calculated by using IAP classification and health status

assessed by PE and quality of life assessed using PedsQL(Pediatric quality of Life Inventory) scale for children between 10 to 17 years of boys .

RESULTS

A total of 100 children orphaned by AIDS living in HIV care giving home in Salem were included in our study.
The study consisted of 100 HIV children. the mean age of the children was 14.53.

1. Demographic profile of the children.
2. Degree of malnutrition of HIV children .
3. Quality of life of HIV children of study participants.
4. Care givers report of study participants.

The Percentage distribution of demographic variables of HIV children, 80% were in the age group of 13-18 years, All are males, 97% of children were in second economic status 47% of children were in second birth order, 53% of children are last their both mother and father 100% of children all are immunized, all are in stage I of who clinical stage, 80 % children were in high school education. 99% of

Nutritional Status

Degree of malnutrition of HIV children: The percentage distribution of degree of malnutrition, of no one in normal , 5% of HIV children were in Grade I, 55% of HIV children were in Grade II, 29% of HIV children were in Grade III, 11% of HIV children were in Grade IV.

Quality of life

In physical functioning , majority of the children problems with walking more than one block of 93% were sometimes in running 99%were in often , in hard to play or sports or exercise 95% were often, in hard to pick up things / lifting heavy 55% were in sometimes. In hard to taking bath 52% were in sometimes , in hard to do chores 55% were in often . in having hurts or aches 50% were in often. In feel too tired to play/low energy level 50% were in often. In emotional functioning , the children having problem with the feel scared 62% had often , in feeling sad 54% well in often , in feel mad/ angry 65% had sometimes . in sleeping 50% of children having often , in worry about what will happen to you 46% had often.

In social functioning , the children having problem with getting along with others 56% had often , in others do not want to play with you 62% had often . in other children can do things that you , 63% had often , in other children can do things that you cannot do 64% had often. In school functioning , the children having problems with paying attention in class 62% were often, in forgetting things 58% were sometimes. in keeping with school because of not feeling well 57% were often , in missing school to go to the doctor or hospital 59% were often.

According to the child report to study participants most of children with HIV having problems of sometimes and almost always. In physical functioning , majority of the children problems with walking more than one block of 99% were sometimes in running 100%were in often , in hard to play or sports or exercise 98% were often, in hard to pick up things / lifting heavy 51% were in sometimes. In hard to taking bath 63% were in sometimes , in hard to do chores 55% were in often . in having hurts or aches 43% were in often. In feel too tired to play/low energy level 72% were in often. In emotional functioning , the children having problem with the feel scared 64% had often , in feeling sad 57% well in often , in feel mad/ angry 55% had sometimes . in sleeping 53% of children having often , in worry about what will happen to you 47% had often.

In social functioning , the children having problem with getting along with others 57% had often , in others do not want to play with you 56% had often . in other children can do things that you , 64% had often , in other children can

do things that you cannot do 67% had often. In school functioning , the children having problems with paying attention in class 52% were often, in forgetting things 43% were sometimes . in keeping with school because of not feeling well 70% were often , in missing school to go to the doctor or hospital 49% were often.

- The table depicts the psychosocial problems of HIV children, out of 100 samples. The following data was analysed.
- With regards in the parent reports none of them had minimal problem, 96% had moderate problem, 4% had severe problem.
- In emotional problems none of them had minimal problem, 74% had moderate problem, 26% had severe problem.
- In social problem, none of them had minimal problem, 82% had moderate problem, 18% had severe problem.
- In school problem, none of them had minimal problem, 58% had moderate problem, 42% had severe problem.
- With regards in the child reports none of them had minimal problem, 99% had moderate problem, 1% had severe problem.
- In emotional problems none of them had minimal problem, 72% had moderate problem,28% had severe problem.
- In social problems, none of them had minimal problem , 89% had moderate problem, 11% had severe problem.
- In school problems, none of them had minimal problem, 68% had moderate problem,32% had severe problem.

CONCLUSION

As the last mile towards ending AIDS for every child approaches, complacency is dangerous. Sustained commitment to refining the response to ensure that all children and adolescents, especially the most vulnerable, are reached by prevention, testing and treatment well into the future is more essential than ever.

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TABLE 1. Demographic profile of the children:

Demographic variables	Percentage
Age	
8 -12 years	20
13-18years	80
Gender	
Male	100
Female	0
Socio economic status	
Upper lower	1
Lower lower	99

Birth order	
First	29
Second	47
Third	24
Parental living status	
Both alive	12
Father death mother alive	17
Mother death father alive	18
Both dead	53
Education	
Middle school	20
High school	80
History of ART	
1-4 years	99
5-8 years	1

Table 2 - Degree of Malnutrition.

Grade	Degree of Malnutrition	
Normal - < 80	Frequency	percentage
Grade -1 71-80	5	5
Grade -2 61-70	55	55
Grade -3 51-60	29	29
Grade -4 < 50	11	11

Table 3 Child Report of Quality of life of HIV children.

PHYSICAL FUNCTIONING (PROBLEMS WITH	never	Always never	Some times	often	Almost Always
Walking more than one block			93.0	7.0	
Running			1	99	
Participating in sports activities			5	95	
Lifting something heavy			55	44	1
Talking a bath or shower by himself or herself			48	52	
Doing chores, like picking up his or her toys			45	55	
Having hurts or aches			49	50	1
Low energy level			50	48	2
EMOTIONAL FUNCTIONING (PROBLEMS WITH...)					
Feeling afraid or scared			33	62	5
Feeling sad or blue			42	54	4
Feeling angry			32	65	
Trouble sleeping			45	50	5
Worrying about what will happen to him or her.			15	46	39

SOCIAL FUNCTIONING (PROBLEMS WITH)					
Getting along with other children			44	56	
Other children not walking to be his or her friend			38	62	
Getting teased by other children			37	63	
Not able to do things that other children his or her age can do			36	64	
Keeping up when playing with other children			36	62	2
SCHOOL FUNCTIONING (PROBLEMS WITH)					
Paying attention in class			36	62	2
Forgetting things			40	58	2
Keeping up with school activities			38	57	5
Missing school because of not feeling well			36	59	5
Missing school to go to the doctor or hospital			19	52	29

Table 4. Care givers report of study participants.

PHYSICAL FUNCTIONING (PROBLEMS WITH	never	Always never	Some times	often	Almost Always
Walking more than one block			99	1	
Running				100	
Participating in sports activities			2	98	
Lifting something heavy			51	49	
Talking a bath or shower by himself or herself			63	35	2
Doing chores, like picking up his or her toys			45	55	
Having hurts or aches			33	43	24
Low energy level			16	72	12
EMOTIONAL FUNCTIONING (PROBLEMS WITH...)					
Feeling afraid or scared			34	64	2
Feeling sad or blue			38	57	5
Feeling angry			55	43	2
Trouble sleeping			45	53	2
Worrying about what will happen to him or her.			11	47	42
SOCIAL FUNCTIONING (PROBLEMS WITH)					

Getting along with other children			41	57	2
Other children not walking to be his or her friend			42	56	2
Getting teased by other children			35	64	1
Not able to do things that other children his or her age can do			28	67	5
Keeping up when playing with other children			33	66	1
SCHOOL FUNCTIONING (PROBLEMS WITH)					
Paying attention in class			48	52	
Forgetting things			43	37	20
Keeping up with school activities			22	70	8
Missing school because of not feeling well			15	66	19
Missing school to go to the doctor or hospital			28	49	23

Table -5 Frequency distribution of quality of life of HIV children (child report)

		Child report		Care giver report	
S.no		Frequency	percentage	Frequency	Percentage
1.	Physical functioning.				
	a) Minimal				
	b) Mild				
	c) Moderate	99	99	96	96
	d) severe.	1	1	4	4
2.	Emotional functioning.				
	a) minimal.				
	b) mild.				
	c) moderate.	72	72	74	74
	d) severe.	28	28	26	26
3.	Social functioning.				
	a) minimal.				
	b) mild.				
	c) moderate.	89	89	82	82
	d) severe.	11	11	18	18
4.	School functioning.				
	a) minimal.				
	b) mild.				
	c) moderate.	68	68	58	58
	d) severe.	32	32	42	42

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REVIEW ARTICLE

A Review on Biopharmaceutical Classification System (BCS)

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ABSTRACT

The Biopharmaceutical Classification System (BCS) has provided a mechanistic framework for understanding the concept of drug absorption in terms of permeability and solubility. This article reviews the criteria and issues for classification of drugs according to the BCS. The present development has enabled us to predict the solubility and permeability character of the drug molecule at early development stages by making necessary structural changes to the molecule to optimize the pharmacokinetic parameters. This article reviews the criteria for classifying drugs according to BCS and discusses further potential applications of BCS, including the development of new drugs and controlled release products.

Keywords: Biopharmaceutical classification system, biopharmaceutical, solubility, drug delivery biowaiver.

INTRODUCTION [1,2,3,4,5,6,7,8]

The Biopharmaceuticals Classification System (BCS) is a systematic structural for classifying pharmaceutical substances based on their aqueous solubility and intestinal permeability. This classification system. This concept underlying the finally published BCS gave rise to the possibility of discounting in vivo bioequivalence (BE) studies in favor of specific comparative in vitro testing to eliminate BE of oral immediate release (IR) effect with structural activity. BCS has gained international recognition in industry, academic institutions and public authorities. The principle of BCS is that if two drug products produce similar concentration profiles along the gastrointestinal (GI) tract, they will result in the same plasma profile following oral administration. The oral route of drug administration is the primarily important method for administering drugs for systemic effects. When a new drug is discovered, one

of the first questions a pharmaceutical company asks is whether the drug can be successfully administered by the oral route for its intended effect. The development of dosage forms specifically for the purpose of prolonged release has been a challenge for scientists, due to the many free factors and competing motives that control drug absorption from the gastrointestinal trac. Action taken to improve one objective or set of objectives may degrade another objective or set of objectives . BCS guidance takes into account three key factors, dissolution, solubility and intestinal permeability, which govern the rate and extent of drug absorption from immediate-release solid dosage forms. BCS has also been involve in difference guidance documents of regulatory importance.

CONCEPT BEHINDBCS [9,10,11,12,13,14,15,16]

The *in-vivo* performance of orally administered drugs depends on their solubility and tissue permeability characteristics. If the absorption permeation rate of the drug is limited and in such cases an in-vitro dissolution study can be used to demonstrate bioavailability (BA) or bioequivalence (BE), then the release rate or solubility of the drug substance is a governing parameter. Won't happen. of drug product via in vitro - in vivo correlation (IVVC). On the other hand, if the absorption dissolution rate of the drug is limited, it means that the drug in the gastrointestinal fluid dissolves freely through the bio-membrane or exceeds the rate of its release from the dosage form. In such a case a specially designed in-vivo study would be needed, to arrive at the absorption rate, and therefore to demonstrate its bioavailability and ultimately bioequivalence. Such a pharmaceutical material is a quality applicant for controlled delivery provided so as they certified in terms of their pharmacokinetics and pharmacodynamics for controlled release development. Furthermore if a drug itself has low solubility and a slow dissolution rate, release will spontaneously be slow and the dosage form does not require an inherent release retardation mechanism, but rather absorption is now controlled by the rate of gastric emptying. Will happen Therefore, the dosage form must be able to be contained within the absorption window for a sufficient time for absorption to occur. In such a case, a hydrodynamically balanced (floating) system or a mucoadhesive dosage form would serve the purpose. Therefore BCS vessels serve as a direct tool for the enlargement of various oral drug delivery technologies.

CHARACTERIZATION OF DRUG MOIETY [17]

For a pharmaceutical substance to be deployed in BCS, its solubility and tissue permeability characteristics must be known:

SOLUBILITY AND DISSOLUTION [18,19,20,21]

Dissolution is a process by which a solid substance (drug) moves into solution, i.e. mass transfer of molecules from a solid surface to a liquid state. Solubility is a property of a substance due to which it forms mixtures with other substances, which are chemically and physically homogeneous. The level of solubility (herein following mention to as "solubility") is the concentration of the solute in a saturated solution (in equilibrium with the solid/drug) at any given temperature. The rate of solubility and solubility are not the same. In contrast to solubility, dissolution rate (that is, the amount of solids that move into solution per unit time under standard conditions of temperature, pH, solvent composition, and constant solid surface area) is a dynamic process and is better related to drug absorption and Bioavailability. However, the rate of dissolution for a pharmaceutical substance is proportionally related to its solubility in the dissolution medium. It has been investigated that unless a compound has an aqueous solubility greater than 1% (10 mg/mL) over the pH range 1–7 at 37 °C, potential bioabsorption problems can occur, and if the internal dissolution rate is less than 1 more than a milligram. /cm2/min then absorption remains undisturbed.

DETERMINATION OF SOLUBILITY [22,23,24,25]

Solubility is determined by exhibit an excess of solid (drug) to liquid (water/buffer) and assessment following equilibrium is accepted. It usually takes 60 to 72 hours to establish equilibrium; It is necessary to sample at earlier points. The solubility cannot be determined by the precipitation method because of the so-called metastable (solubility) region. The pH solubility profile of the drug is determined in aqueous medium at 37 ± 10 °C, the pH is in the range of 1-7.5. A sufficient number of samples should be assess to correctly define the pH solubility profile. A

minimum of three duplicate establishment of solubility must be made at each pH condition. Standard buffer solutions report in the Pharmacopoeia (BP 2003) are observe acceptable for use in solubility studies. The concentration of the drug substance in the selected buffer or pH condition must be determined using a validated solubility-indicating assay that can separate the drug substances from their degradation products.

DETERMINATION OF PERMEABILITY [26,27,28,29,30,31]

Routinely used methods for the determination of permeability include the following:

a. Pharmacokinetic studies in human subjects including group balance studies and complete bioavailability (BA) studies or intestinal permeability methods

b. In vivo or in situ intestinal perfusion in a acceptable animal model

C. In vitro permeabilization methods using stimulated intestinal tissue

D. Monolayers of suitable epithelial cells e.g. Caco-2 cells orTC-7 Cell

In mass stability studies, unlabeled, stable isotope or radiolabeled drug substances are used to determine the extent of drug absorption. In absolute BA studies, oral BA is determined and compared against intravenous BA as a reference. Intestinal perfusion models and in vitro methods are submit for inactive transported drugs. An interesting alternative to the intestinal tissue model is the use of an in vitro system based on the human adenocarcinoma cell line Caco-2. These cells serve as models of small intestine tissue. Differentiated cells display integral membrane proteins of the small intestinal mucosa typical of microvilli and brush-border enzymes. They also form the fluid-filled dome typical of permeable epithelium. Recent exploration of Caco-2 cell lines have designate their capacity to transport ions, sugars and peptides. These properties have accepted the Caco-2 cell line as a dependable in vitro model of the small intestine.

Classification

According to the drug substance are classified in four different class as shown in figure:

Class I: High solubility, High permeability: Normally very well absorbed particle

Class II: low solubility, high permeability: performance dissolution rate-limiting absorption

Class III: High solubility, low permeability: Performance permeability-limited absorption

Class IV: Low solubility, Low permeability: especially poor oral bioavailability

Class I : High Solubility - High Permeability Normally very well absorbed particle[32,33,34,35,36]

In-vivo these drugs behave like oral solutions with rapid dissolution and rapid bioavailability. Since the dissolution and absorption of first-class drugs are very rapid, the bioavailability and bioequivalence for such drug products is meaningless. These drugs are good candidates for controlled drug delivery if they are pharmacokinetic associates and pharmacodynamically qualified to the point. In this case gastric emptying is often the rate controlling the threshold. Class I drug molecules are not those in which either solubility or permeability is limited within target areas of the GI tract. In such cases the drug molecules to be released can be modified using a controlled release technique. Controlled release technologies for Class I drug molecules include multiporous oral drug absorption systems, single composition osmotic tablet systems, microsphere, constant surface area drug delivery shuttles, diffusion controlled matrix systems, delayed pulsatile hydrogel systems, dual release drug absorption systems, and many more Are included. Granular Modulating Hydrogel System, Intestinal Protection Drug Absorption System, Microparticle Drug Delivery Technology, Pelletized Pulsatile Delivery System, Bioerodable Enhanced Oral Drug Absorption System, Programmable Oral Drug Absorption System, Spheroidal Oral Drug involement system, insoluble regulate alginate system, and SustainPellet Delivery System.

Class II : Low Solubility - High Permeability; exhibit dissolution rate limiting absorption [37,38]

Drug molecules have low solubility and high permeability, therefore, the dissolution rate becomes the key parameter for bioavailability. These drugs reveal variable bioavailability and improving the bioavailability requires improvement of dissolution rates by various means. These are also acceptable for controlled release development. Technologies under this class include approaches such as classical micronization, immobilization of high-energy

states (including lyophilized fast-melt systems), surfactant, emulsion or microemulsion systems, solid dispersions, and the use of a complexing agent such as cyclodextrin.Technologies receive that class involve: soft gel (soft jelly capsule expression), Zer-OS tablet technology (osmotic systems), triGlas and nanosized carriers such as nanoemulsions, nanosuspension and nanocrystals as an optimistic means of increasing the solubility and BA of poor water. regarded as. - soluble active ingredients.

Class III: High Solubility-Low Permeability; exhibit permeability-restricted absorption [39,40]

Drug molecules of this class form the rate-determining step for these drug molecules through the intestinal membrane. Since the absorption permeation rate is limited, bioavailability is self-regulating of drug release from the dosage form. For example, different ranitidine result with different dissolution profiles manufacture superimposable plasma concentration versus time profiles in vivo. These drugs usually show low bioavailability and usually need to increase permeability. These drugs are testing for controlled enlargement.

Class IV: Low Solubility – Low Permeability; especially poor oral bioavailability [41,42]

Drug molecules of this class show poor and unpredictable bioavailability. Bioavailability is generally controlled by several factors such as rate of dissolution, intestinal permeability, gastric emptying, and so on. These drugs are generally not suitable for oral drug delivery or some specialized drug delivery technologies such as nano-suspension would be desirable.

Biowaivers [43,44,45,46,47]

The term biowaiver is especially functional in the regulatory drug acceptance activity when the dossier (application) is approved based on evidence of equivalence other than an in vivo equivalence test. Bioweaver means getting discounts for studying expensive and time consuming BA and BE. A bioequivalence has been considered as official acceptance of exemption to conduct a bioequivalence study in the context of an application for the Drug Molecules Approval Process. Related to BCS-based Bioweavers Pre-(IND/NDA & ANDA), Post-approval stage. BCS-based bioweavers are relevant for immediate-release solid oral drug formulations that contain one or more of the APIs described above if the required data ensures equivalence of the submitted pharmaceutical product and an appropriate pharmaceutical equivalent comparator product. BCS-based bioweavers have become an important and cost-saving tool in the approval of basic (generic) drugs (FDA Guidance 2000)Currently BCS Class I drugs and some Class III drugs are suitable for bioweavers. The drug molecules must be highly soluble and highly permeable. An IR pharmaceutical product should dissolve quickly. The drug molecules should not be a drug of a narrow therapeutic index. The excipients used in the dosage formulation must have been used in the IR solid dosage form previously approved by the FDA. Used for relaxation of in vivo relative bioavailability studies, dissolution in 30 minutes in three recommended dissolution media (acidic media, such as 0.1 N HCl or Simulated Gastric Fluid USP, pH 4.5 buffer without enzymes) exceeds 85% needed; and a pH 6.8 buffer or simulated intestinal fluid without enzymes (USP). In vivo bioequivalence, used for testing and relaxation of reference products, should exhibit similar dissolution profiles under the defined dissolution test conditions for rapidly dissolvingproducts .

Aim of BCS Guidance [48,49,50,51]

- To predict the in vivo performance of pharmaceutical products from in vitro measurements of permeability and solubility
- To improve the efficiency of the drug development and review process by recommending a strategy for the identification of expendable clinical BE trials.
- Recommending methods of classification according to the solubility, permeability characteristics of the drug product as well as the dosage form dissolution.
- Providing regulatory tools to replace some bioequivalence studies by precise in-vitro dissolution tests.
- This will reduce the cost in drug development process, also reduce unnecessary drug exposure in healthy items.
- Providing guidance to the industry.

Basic Requirements of BCS[52,53]

- It should predict the in-vitro dissolution system well.
- The rate limiting step for in-vivo absorption should be well defined.
- The range of permeability and solubility must be balanced.
- *In-vitro* methods must be adequately strong for accurate classification.

Thoughtful Boundaries of BCS [54,55,56]

- absorption carrier and stream pumps are not observe.
- Medicines that are undergoing first pass metabolism or secondary metabolism are not factored in appropriately.
- The solubility and permeability measurements are loosely defined.
- Food effect is not considered.
- Possibility of misclassification.
- This is based on the highest dosage but..(what about smaller doses of the same product?)
- Intended only for immediate release (IR) products that are absorbed throughout the GIT.

Applications of biopharmaceutics classification system

Drug delivery technologies

Class I systems [57,58,59,60]

Class I drugs are not those in which either solubility or permeability is limited within target areas of the GI tract. In such cases the drug release can be modified using a controlled release technique. Controlled release technologies for Class I drugs include a number of products such as Macrocap, Micropump, etc.MODIS (uniparous Oral Drug involvement System), SCOT (Single Constitution Osmotic Tablet System), Microsphere, Consurf (Constant Surface Area Drug Delivery Shuttle), Diamatrix (Diffusion Controlled Matrix System), DPHS (Delayed Pulsatile Hydrogel System), DUREDAS (Dual Release) drug absorption system), GMHS (granulated modulating hydrogel system), IPDAS (intestinal protective drug absorption system),Multipore, Pharmazone (Microparticle Drug Delivery Technology), PPDS (Pelletized Pulsatile Delivery System), BYODAS (Bioradiable Enhanced Oral Drug Absorption System), Produs (Programmable Oral Drug Absorption System), SODA (Spheroidal Oral Drug Absorption System), SMHS (Solution Modulating System)) Hydrogel System) and SPDS (Stabilized Pellet Delivery System).

Class II systems [61,62,63]

This class belongs to instance in which the insoluble or termination rate is restricted, and thus importantly influnce absorption and BA. Technologies under this class include approaches such as classical micronization, immobilization of high-energy states (including lyophilized fast-melt systems), surfactant, emulsion or microemulsion systems, solid dispersions, and the use of a complexing agent such as cyclodextrin. Technologies under this class include: softgels (soft gelatin capsule formulations), Zer-OS tablet technology (osmotic systems), trigels and nanosized carriers such as nanoemulsions, nanosuspensions and nanocrystals as optimal means of increasing solubility and BA of spoiled water. Contains - Soluble Active Ingredients.

Class III systems [64]

Modulating the metabolic activity of the enzyme system by the site or rate of exposure or perhaps by adding functional agents as dosage forms are included in Class III technologies. Technologies that drop under that class involve oral vaccine systems, intestinal retention systems, high-frequency capsules, and telemetric capsules.

Class IV systems [65]

Greatest examples of class IV combination are the deviation rather than the rule and are infrequently developed enough to reach the market. But number of examples of class IV drugs exist, for example, cyclosporine A, furosemide, ritonavir, saquinavir, and Taxol.

CONCLUSION

In conclusion, the in vivo pharmacokinetics of drugs largely depends on solubility and permeability. BCS own proven to be an especially useful direct instrument for the prediction of the in vivo performance of drug substances and the development of new drug delivery systems tailored to drug performance in the body, as well as for the regulation of drug bioequivalence. Products during scale-up and post approval. In the future, the BCS concept will likely be increasingly used in the first development of new drugs, including double selection as well as first formulation approaches.

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Table : 1 High Solubility & Low Solubility [32,37,39,41]

	HighSolubility	**Lowsolubility**
High Permeability	**ClassI** High Solubility High Permeability Eg: Buspirone Ketorolac Chlorpheniramine	**ClassIII** Low solubility High Permeability Eg:*Acyclovir* *Amiloride* Amoxicillin
Low Permeability	**ClassII** High Solubility Low Permeability Eg: Amiodarone AtorvastatinAzithromycin	**ClassIV** Low solubility Low Permeability Eg: Amphotericin B Colistin Ciprofloxacin

Table : 2 Examples of some drugs as per biopharmaceutical classification system [34,36,38,40]

Class I	**Class II**	**Class III**	**Class IV**
Chloroquine	Carbamazepine	Acyclovir	CoenzymeQ_{10}
Diltiazem	Danazol	Atenolol	CyclosporinA
Metoprolol	Glibenclamide	Captopril	Ellagicacid
Paracetamol	Ketoconazole	Cimetidine	Furosemide
Propranolol	Nifedipine	Metformin	Ritonavir
Theophylline	Phenytoin	NeomycinB	Saquinavir
Verapamil	Troglitazone	Ranitidine	Taxol

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RESEARCH ARTICLE

Big Data Analytics using R Tool: A Survey

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ABSTRACT

Big data analysis has exponential growth and will certainly continue to witness spectacular developments due to the emergence of new interactive multimedia applications and highly integrated systems driven by the fast growth in information services and microelectronic devices. Most of the current mobile systems can mainly be targeted to voice communication with low transmission rates. In the future, however, big data access at high transmission rates will be. This is a review of accessible big data systems that include a set of tools and techniques to load, extract, and improve dissimilar data while leveraging the immensely parallel processing power to perform complex transformations and analysis. Big Data system faces a series of technical challenges. R is an open-source data analysis an environment, and programming language. The process of converting data into knowledge, insight, and understanding is Data analysis, which is a critical part of statistics? The effective processing and analysis of big data, allows users to conduct several essential tasks. R contains numerous ready-to-use statistical modeling algorithms and machine learning which allow users to create reproducible research and develop data products. Although big data processing can be accomplished with other tools as well, it is when one steps on to the data analysis that R stands unique, owing to a large amount of built-in statistical formulae and third-party algorithms available.

Keywords: Big Data, R Tool, Big data Analytics, Decision tree, Support Vector Machines

INTRODUCTION

A statistical analyses package named S was developed by Bell Labs in the States. Later in 1994, Ross Ihaka and Robert Gentleman wrote the first version of S at Auckland University and coined it R. The R is an open-source implementation of S and differs from S largely in its command-line. In statistical analyses, R has a broad set of facilities that have been specially constructed. As a result, R is said to be a very powerful statistical programming language tool. The open-source nature of R indicates that, as new techniques for statistics are established, new packages for R usually become freely available very soon after. It consists are own inbuilt statistical algorithms the sheer amount of machine learning algorithms and mathematical models available to users in R and third-party packages is staggering and continues to grow. The R can also carry out important analyses that are difficult or next to impossible in many other such packages, including Generalized Additive Models, Linear Mixed Models, and Non-Linear Models. R contains a broad range of graph drawing tools, which makes it easy to produce standard graphs of your data?. In traditional analysis, developing a statistical model takes additional time by performing the calculation by the computer. In the case of Big Data, this proportion is turned upside down. Big Data comes into the picture when the Central Processing Unit time for the calculation takes longer than the process of designing a model. Data sets that contain up to millions of records can easily be processed with standard R. Data sets are one million to one billion records can also be handled in R, but requires some additional effort. Worldwide, millions of statisticians, as well as data scientists, use R to solve their most challenging problems in the field, right from quantitative marketing to computational biology. R has become the most popular language for data science and the most essential tool for analytics-driven companies such as Facebook, Google, Linked In, and Finance.

The emerging Big Data Science term, which shows its broader impact on our society and in our business life cycle, has insightfully transformed our society and will continue to attract diverse attention from technical experts and as well as the public in general [1] [2]. It is obvious we are living in the Big Data era, shown by the sheer volume of data from a variety of sources and its rising rate of generation. An IDC report predicts from 2005 to 2020, the global data dimensions will grow by a factor of 300, from 130 Exabytes to 40,000 Exabytes, representing a double growth every two years. This is focused on accessible big data systems that include a set of tools and techniques to load, extract, and improve dissimilar data while leveraging the immensely parallel processing power to perform complex transformations and analysis. “Big-Data” system faces a series of technical challenges, including:

First, due to the large variety of different data sources and the large volume, it is too difficult to collect, integrate, and analysis of “Big Data” with scalability from scattered locations. Second “Big Data” systems need to manage, store and integrate the gathered large and varied verity of datasets, while providing function and performance assurance [1], in terms of fast retrieval, scalability, and secrecy protection. Third “Big Data” analytics must effectively excavate large datasets at different levels in real-time or near real-time - including modeling, visualization [2], prediction, and optimization such that characteristic potentials can be revealed to improve decision making and acquire added advantages.

To address these challenges, the researcher IT industry and community has given various solutions for Big Data science systems in an ad-hoc manner. Cloud computing can be called the substructure layer for Big Data systems to meet certain substructure requirements, such as cost-effectiveness, resistance [2], and the ability to scale up or down. Distributed file systems and NoSQL databases are suitable for persistent storage and the management of massive scheme-free datasets [1]. The Map Reduce, R is a programming framework, has achieved great success in processing Big Data group aggregation tasks, such as website ranking [10]. Hadoop integrates Data storage, Data processing, System management, and Other modules to form a powerful system-level solution, which is becoming the mainstay in handling “Big Data” challenges. We can build various “Big Data” application systems based on these innovative technologies and platforms. In light of big-data technologies, a systematic framework should be to capture the fast evolution of big-data research[27] [28].

Big Data Analytics

Business value is not generated by stored data and this is true for traditional databases, data warehouses, also for new technologies like Hadoop for storing big data. Once the data is properly stored, it can be analyzed, and thus immense value can be created. In-memory analytics, database analytics, and a variety of analysis, technologies, and products have arrived that are mainly applicable to big data.

A History of Big Data

In the 1970s, to support decision-making, Decision Support Systems (DSS) were the first systems. DSS used an academic discipline and description for an application. Completed time, additional decision support applications like Executive Information Systems, Dashboards, scorecards as well as OLAP (Online Analytical Processing) became popular. In the 1990s, an analyst at Gartner, Howard Dresner, promoted the term business intelligence. Business intelligence is a process driven by technology for data analyzing and offering actionable information to aid corporate executives, business managers, and other end-users to construct more informed business decisions. The third clarification is that analytics is the use of machine learning algorithms to analyze data. It is useful to compare three kinds of analytics as the dissimilarity indicates the architectures and technologies used for big data analytics.

Considering the growth and complexity of Big Data science systems, previous descriptions are based on a one- side viewpoint, such as chronology or milepost technologies. The history of Big Data is presented in terms of the data size of interest. Under this framework, the history of Big Data is tied closely to the capability of efficiently storing and managing larger datasets, with size boundaries expanding by orders of degree[27][28]. The first one is Megabyte to Gigabyte: In the 1970s and 1980s, historical business data introduced the earliest Big Data challenge in moving from megabyte to gigabyte sizes [18]. The second one is Gigabyte to Terabyte: In the 1980s, the popularization of digital technology caused data volumes to expand to several gigabytes or even a terabyte, which is beyond the storage and/or process capability of a single large computer system? [2]. Data parallelization is proposed to extend storage capacity and to improve performance by distributing data and related tasks, such as building indexes and evaluating queries, into disparate hardware. The third one is Terabyte to Petabyte: During the 1990s, when the database community was admiring its finished work on the parallel database, the rapid development of Web 1.0 led the whole world into the Internet era[2], along with massive semi-structured or unstructured web pages holding terabytes or Peta Bytes (PBs) of data.

Big Data Problem and Challenges

These are probably the biggest challenges R faces. Similarly, people coming to R from other languages might also consider R odd. For all of its benefits, R has its share of shortcomings as follows- Memory, management, Speed, and Efficiency. When working with a very large amount of data sets the design of the language can sometimes lead to problems. Data can be stored in physical memory. This can become a minor issue, as nowadays computers have sufficiently of memory. Ability such as security was not built into the R tool. Similarly, the R tool cannot be embedded in a Web browser. It cannot use it for Web-like or Internet-like apps. It was primarily next to impossible to use the R tool as a backend server to perform calculations due to lack of security over the Web. For a long time, there was not a lot of interactivities in the language. Languages such as JavaScript still have to enter in to fill this gap. Although an analysis may be done in R, the furnishing of results might be accomplished in a different language like JavaScript.

However, considering a variety of a large number of data sets in Big Data problems, it is still a big challenge for us to purpose efficient representation, access, and analysis of shapeless or semi-structured data in further researches [12]. How can the data be preprocessed to improve the quality of data and analysis results before we begin data analysis? [1] [2]. As the sizes of a large number of data sets are often very large, sometimes several gigabytes or more, and their origin from varied sources, current real-world databases are pitilessly susceptible to inconsistent, incomplete, and noisy data. Therefore, several data preprocessing techniques, including data cleaning [11], data integration, data

transformation, and data reduction, can be applied to remove noise and correct irregularities. Different types challenges arise in each sub-process when it comes to data-driven applications.

Principles for Designing Big Data System

In designing Big Data analytics systems, we summarize seven necessary principles to guide the development of this kind of burning issue [3]. Big Data analytics in a highly distributed system cannot be achievable without the following principles are [13]: Good architecture and frameworks are necessary and on the top priority, support a variety of analytical methods, No size fits all, Bring the analysis to data, Processing must be distributable for in-memory computation, Data storage must be distributable for in-memory storage and Synchronization is needed between processing, and data units.

Big Data Opportunities

The bonds between Big Data and knowledge unseen in it are highly critical in all areas of national priority. This creativity will also lay the groundwork for complementary Big Data activities, such as Big Data substructure projects, platforms development, and techniques in settling complex, data-driven problems in sciences and engineering. The Researchers, Policy, and Decision-makers are recognize the potential of harnessing Big Data to uncover the next wave of growth in their fields. Many advantages in a business sector can be obtained through harnessing Big Data increasing operational efficiency, informing strategic direction, developing better customer service, identifying and developing new products and services, recognizing new customers and markets, etc.,

Big Data Analysis

The last and most important phase of the Big Data value chain is data analysis, the goal of which is to get useful values, suggest the best conclusions, and support the decision-making system of an organization to stay in a competitive market. [1]

Descriptive Analytics: Exploits past data to describe what occurred in past. For instance, a regression technique can be used to find simple trends in the datasets, visualization presents data in a meaningful fashion, and data modeling is used to collect, store and cut the data in a well-organized way. Descriptive analytics can be typically associated with business intelligence or visibility systems [2].

Predictive Analytics: Focuses on predicting future probability and trends. For example, a predictive model uses statistical techniques [6] such as linear and logistic regression to understand trends and predict future outcomes, and data mining extracts patterns to provide insight and forecasts [4].

Prescriptive Analytics: addresses decision-making and efficiency. For example, the simulation is used to analyze complex systems to gain insight into system performance and identify issues and optimization techniques are used to find good solutions under given constraints.

Big Data Classification Algorithm

The Big Data Classification algorithm is Decision Tree, Random Forest, and Support Vector Machine

Decision Tree is one of the predictive modeling approaches applied in statistics, data mining, and machine learning. Decision Tree models where target variables can take a finite set of values are called classification trees. The tree structures, leaves represent class labels and branches represent conjunctions of features that lead to those class labels. It is where the target variable can take continuous values are called regression trees. Indecision analysis, can be used to visually and explicitly represent decision making. In the decision tree describes data but not decisions; rather the resulting classification tree can be input for decision making [23].

Random Forests is a collective learning method also thought of nearest neighbor predictor for classification and regression that construct several decision trees at training time and output the class that is the mode of the classes output by the separate tree. Random Forest is a combination of tree predictors where each tree depends on the values of a random vector sampled independently with the same distribution for all trees in the forest. The basic opinion is group of weak learners can come together to form a strong learner. Random Forests are a wonderful tool for making predictions considering they do not over fit because of the law of large numbers. Introducing the right kind of chance makes them correct classifiers and repressors[24].

Support Vector Machines (SVM) is a supervised learning method used for classification and regression tasks that originated from statistical learning theory. The entity space is divided in a single pass so that flat and linear partitions are generated. SVM is based on maximum margin linear discriminates and is similar to probabilistic approaches, but does not consider the dependencies among attributes. The traditional Neural Network(TNN) approach has suffered difficulties with generalization, producing models which over fit the data as a consequence of the optimization algorithms used for parameter selection and the statistical measures used to select the best model. SVMs have been gaining popularity due to many attractive features and promising empirical performance. The Structural Risk Minimization (SRM) principle has shown to be superior to the traditional principle of Empirical Risk Minimization (ERM) employed by conventional Neural Networks. ERM minimizes the error on the training data, while SRM minimizes an upper bound on the expected risk. According to, SVM relies on preprocessing the data to represent patterns in a high dimension, typically much higher than the original feature space. Data from two categories are always be separated by a hyper plane when appropriate non-linear mapping to a sufficiently high dimension is used.[25]

Big Data Tools: Techniques And Technologies

To capture the value from Big Data, we need to develop new techniques and technology for analyzing it. Until now, scientists have developed a wide variety of techniques and technology to capture, accurately, analyze, and visualize Big Data. We need tools to make sense of Big Data. Current tools are concentrated on three classes, namely, batch processing tools, stream processing tools, and interactive analysis tools. Most batch processing tools are based on the Apache Hadoop infrastructure, such as Map Reduce [4], R Programming, and Dryad. An interactive analysis processes the data in an interactive environment, allowing users to undertake their analysis of information.

R Programming

The R language is well established as the language for doing statistics, data analysis, data-mining algorithm development, stock trading, credit risk scoring, market basket analysis, and all [9] manner of predictive analytics. However, given the deluge of data that must be processed and analyzed today, many organizations have been reticent about deploying R beyond research into production applications. [16]

LITERATURE SURVEY

Big Data is a challenge related to volume, velocity, and variety. Big Data is a 3Vs Volume means a large amount of data, Velocity means data arrives at high speed, Variety means data comes from heterogeneous resources. Big Data means a dataset that makes data concepts grow so much that it becomes difficult to manage them by using existing data management concepts and tools. Map Reduce is playing a very significant role in process of Big Data. The main objective of purposed a tool like Map Reduce is elastic scalable, efficient, and fault-tolerant for analyzing a large set of data, highlights the features of Map Reduce is a comparison of another design model which makes it a popular tool for processing large scale of data. A study of performance factors of Map Reduce shows that elimination of their inverse effect by optimization improves the performance of Map-Reduce [3]. Authors can present a literature survey and system tutorial for big data analytics platforms, aim to provide an overall picture for non-expert readers and instill a do-it-yourself spirit for advanced audiences to customize their big-data solutions. It presents the definition of

big data and discusses big data challenges. The current systematic framework decomposes big data systems into four sequential modules, namely data generation, data acquisition, data storage, and data analytics. These four modules are big data value chains. The present a detailed survey of numerous approaches and mechanisms from research and industry communities. The main objective of this paper is purposed a model scalable system for Big Data analysis [2].

In the Big Data community, Map Reduce has been seen as one of the key enabling approaches for meeting the continuously increasing demands on computing resources imposed by massive data sets. At the same time, Map Reduce faces several obstacles when dealing with Big Data including the lack of a high-level language such as SQL, challenges in implementing iterative algorithms, ad-hoc data exploration, and stream processing. The identified Map Reduce challenges are grouped into four main categories corresponding to Big Data tasks types: data storage, analytics, online processing, security, and privacy. The main objective of this paper is to identify Map Reduce issues and challenges in handling Big Data to provide an overview of the field, facilitate better planning and management of Big Data projects, and identify opportunities for future research in this field [4].

Micro architectural characteristics of data analysis workloads, also finding that they exhibit different characteristics from traditional workloads. Performance and power consumption using hybrid big data workloads. Continuing the work in a group releases the multi-tenancy version of Big Data Bench, which supports the scenarios of multiple tenants running heterogeneous applications in the same data center. The multi-tenancy version of Big Data Bench is publicly available, which is helpful for the research of data center resource management and other interesting issues. Much work focuses on comparing the performance of different data management systems. Cooper define a core set of benchmarks and report throughput and latency results for five widely used data management systems [5].

A large number of fields and sectors, ranging from economic and business activities to public administration, from national security to scientific researches in many areas, are involved with Big Data problems. Big Data is very valuable to produce productivity in businesses and evolutionary breakthroughs in scientific disciplines, which give us a lot of opportunities to make great progress in many fields. The main objective of this paper is to emphasize the significance and relevance of Big Data in our business system, society administration, and scientific research. They have purposed potential techniques to solve the problem, including quantum computing, cloud computing, and biological computing [1].

CONCLUSION

Big Data problems are still having a big challenge for us to purpose efficient representation, access, and analysis of shapeless or semi-structured data in more researches. For this, to apply a different classification technique, choose a real dataset about the student's knowledge status about the subject of Electrical DC Machines. The circulation of every numeric variable can be check with function summary( ), which returns the minimum, maximum, mean, median, and the first (25%) and third (75%) quartiles. In Categorical Variables, it shows the frequency of every level. It creates a powerful and reliable statistical model, data transformation, evaluation of multiple model options, and visualizing the results are essential. This is the reason why the R tool language has proven so popular: its interactive language uplifts exploration, clarification, and presentation. Revolution R Enterprise gives the big-data support and speed to allow the data scientist to repeat this process quickly[27][28].

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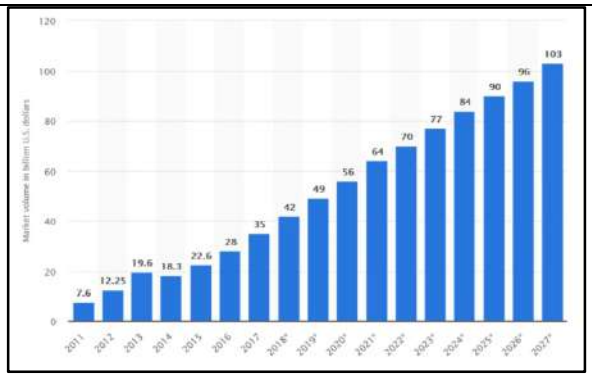

Source: Primary Data

Figure 1: Growth of Big Data

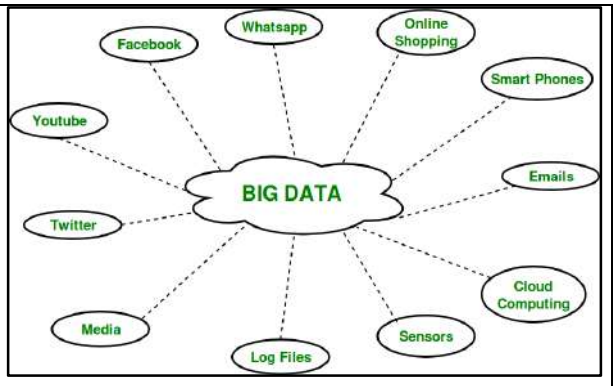

Figure 2: Source of Big Data