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Message from the Chief Mentor & Managing Trustee

With profound pleasure, I present to you the 10th issue of the NSHM Journal of Pharmacy & Healthcare Management. The Journal brings together research on the practice of pharmacy along with research on the education and development of the pharmacy workforce and its impact on pharmacy healthcare delivery system. Pharmacy covers the full spectrum of translational science where basic science research is translated into new methods of diagnosis, treatment and prevention of diseases in humans. The Indian healthcare system has undergone phenomenal transformation in the past few decades with commendable advancements in various research fields. Our vision is to promote research that will be helpful for sharing knowledge, new discoveries, development of critical thinking among the upcoming scholars.

The NSHM Journal of Pharmacy & Healthcare Management emphasizes on high quality original research articles besides encouraging reviews and short communications. It is a matter of pride for us to have excellent editorial board members from renowned institutes.

As chief mentor, I am honoured to serve and contribute to the knowledge leadership of the organization in such a meaningful way. I look forward to helping NSHM to produce high quality scientific research that is recognized by the academia and industries around the world for its impact.

I express my heartfelt best wishes to the Director and all the esteemed faculty members for their joint effort to make this journal a world class journal of global standing.

*Mr. Cecil Antony
Chief Mentor & Managing Trustee
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Message from the Desk of Chief Editor

It is with profound pleasure, humility and anticipation that we celebrate the launch of 10th volume of the NSHM Journal of Pharmacy and Healthcare Management (NJPHM), the official journal of NSHM Institute of Health Sciences (NIHS), NSHM Knowledge Campus - Kolkata.

NSHM Institute of Health Sciences is known for its academic excellence and dedicated approach towards dissemination of knowledge in the academic world. The Institute appreciates the role of research in education and is committed to developing an inclination towards research in both faculty and students. In this continuous pursuit, NIHS has taken the initiative to launch the 10th volume of NSHM Journal of Pharmacy and Healthcare Management.

It is the annual Journal launched exclusively to publish academic research papers and articles by the students, faculty & industry personnel on contemporary topics and issues in the area of Pharmaceutical Technology, Dietetics & Nutrition, Public Health and allied healthcare sectors.

NSHM Journal of Pharmacy and Healthcare Management provides an ideal forum for exchange of information on all of the above topics and beyond.

In order to maintain high standards of publication, an editorial board has been constituted, which is the apex authority to take all decisions related to publication of research papers and articles in NJPHM.

To maintain high academic standards, academic ethics and academic integrity, a process of review is followed along with screening of plagiarism of each manuscript received by the editorial board for publication.

I congratulate all the contributors whose research / review papers are published in this volume of NJPHM and express my sincere thanks to their mentors and referees. Further, I also extend my heartfelt gratitude to all, who have volunteered to contribute to the success of the journal.

***With Best Wishes,
Prof. (Dr.) Subhasis Maity
Chief Editor
Director, NSHM Institute of Health Sciences,
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Cross-tolerance of bacteria to structurally unrelated stress factors

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Abstract :

Bacteria are challenged with different types of stress conditions (e.g. high and low temperature, low pH, high salt) in the natural environments, inside our body and also in the freezer compartments used for the storage of food materials. Exposure to sub-inhibitory doses of these stressors may be associated with tolerance of the organisms to higher dose of the same stressor and sometimes resistance to a different stress condition. Implication of these phenomena in food safety and antibiotic therapy is discussed with relevant examples.

Introduction

Bacteria are unicellular organisms present everywhere in nature. They cannot run or fly when confronted with unfavorable environments. They have to withstand freezing sub-zero temperature of the glaciers, high temperature of the hot springs, high pressure of the sea bottom and desiccating environment of the dried-up lakes when they happen to be there. Small intestine is the preferred niche of *Salmonella typhi* (the bacterium that causes typhoid) in the human body. But before reaching there after gaining entry into the body through contaminated food and drink, the pathogen has to survive the highly acidic pH of the gastric juice, when passing through the stomach. The ability of bacteria to adapt to the extreme environments makes some of them useful for different types of biotechnological purpose [1]

The unfavorable conditions (high or low temperature and pH, high salt, dehydration, high pressure, ionizing radiation) not conducive for the sustainment of life, are called stress factors (or stressors). Bacteria are challenged with multiple stressors in the outer environment. As a matter of fact, the stressors seldom occur alone in nature. They occur mostly in various combinations. Antarctica is very cold and very dry. So bacteria present there have to be cold-tolerant and desiccation-tolerant. Water in many hot springs is acidic. Hence, bacteria isolated from that water, have to be heat-tolerant and acid-tolerant. Similarly, bacteria in the sea bottom have to cope with high salinity and high pressure. Bacteria are all-pervading. Hence they are endowed with the capacity to tolerate more than one environmental stressor. Accumulating evidences suggest that some bacteria might evolve with molecules that enable them to adapt to multiple stressors. Biotechnological potential of these multi-stress combatants appears to offer a challenging field for scientific investigation [2-3].

Existence of bacteria is threatened by various types of stressors not only in the natural environment. When we preserve food in cold, we also subject the different types of bacteria present in the food materials, to low temperature of the freezer compartment. Further, in order to ensure total arrest of bacterial growth during preservation, we add salt and organic acid (in the form of lemon juice) to the food materials. Thus, bacteria in the food are challenged with multiple stressors (low temperature, high salt, low pH). Nature endows them with the capacity to adapt to these stressors. Unfortunately, this adaptability does not augur well with our well-being. Let us see why.

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Stress- hardiness and Cross-tolerance

It is a fact that even from the well-preserved food materials, live bacteria are isolated from time to time. So there is no doubt that despite our best possible effort, bacteria present in the food cannot be totally annihilated. Like their naturally-occurring cousins, they also adapt to the stressors inflicted upon them by us. When adapted to the low dose of one stress factor, they develop resistance to the higher dose of the same stressor. The phenomenon known as stress hardiness makes it difficult for us to ensure safety in consumption of the preserved food materials. It may not be possible for us also to use the stressors (salt, organic acid) in the correct amount to completely arrest the growth of the contaminating bacteria. The food bacteria in presence of sub-inhibitory concentrations (SICs) of the stressors, develop tolerance also to some structurally-unrelated stressors. It is called cross-tolerance. Thus, while preserving food in cold with salt and acid, we may inadvertently help food bacteria in developing tolerance to (or getting trained to survive in presence of) more than one growth-inhibitory substance [4]

Antibiotics as Stressors

It is observed that antibiotics are also sensed as stressors by bacteria. Exposure of a bacterial population to the SICs of antibiotics induces stress-hardiness and cross-tolerance in them. On the other hand, some environmental stressors (detergents, organic solvents, dyes, food components, preservatives) induce a group of genes. Some of them trigger expression of at least one broad-range efflux pump that helps the bacterial cells to get rid of various types of unfavorable substances (including antibiotics) by pushing them out of the cells. So even in our daily life, we are unknowingly exposing bacteria to some substances that help them overcome the challenge of antibiotics [4].

Bacteria in our body get exposure to the SICs of antibiotics in various ways. In this context, it appears worthwhile to remember the concern voiced by Sir Alexander Fleming, the discoverer of penicillin, in his Nobel Lecture (delivered at Stockholm on December 10, 1945) “The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily under-dose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant”. The world-famous scientist no doubt foresaw what is happening in our country at present. We take antibiotics for trifle illness (e.g, common cold) on self-prescription and also following the advice of the “experienced” owners of the local pharmacy. When we fall ill, most often we approach these quacks, instead of seeking advice from a qualified doctor. We do not complete the course of antibiotics once symptoms of illness disappear. Moreover, antibiotics are added to the animal feed in farms to prevent infection of the livestock and also to promote their growth. So their flesh used as our food, may contain low amount of antibiotics [5]. Exposure to the SICs of antibiotics may trigger the production of Reactive Oxygen Species (ROS) in the bacterial cells. ROS may induce mutation thereby enhancing the possibility of emergence of the antibiotic-resistant varieties in the bacterial population [6]. The SICs also promote a process called horizontal gene transfer that enables antibiotic-tolerant bacteria to transfer copies of the resistance-conferring genes to unrelated bacteria present in their surroundings. Thus, the ability of bacteria to adapt to the stressors appears problematic to us in multiple ways.

Studies on Cross-resistance : Some examples

A team of researchers at the University of Ulster, (Northern Ireland, UK) found increase in antibiotic-resistance in some bacteria (*Salmonella enteric* serovar *Typhimurium*, *Escherchia coli* and *Staphylococcus aureus*) following incubation under increased salt (>4.5%) or reduced pH (<5.0). The organisms were sampled from various types of food materials (raw mussels, chicken and egg mix/fried rice) and also from swabs taken from commercial food kitchens. However, antibiotic-resistance was decreased following incubation at 45°C that was a sub-lethal temperature for the bacteria [4]. Two scientists at the Department of Biochemistry, The Hong Kong University of Science and Technology, observed when some *E.coli* cells were preserved at -80°C, most of the cells died. But when they were heated at a sub-lethal temperature for a brief period of time before cold preservation, the rate of recovery was substantially improved [7]. Similar investigations were performed some time back, as a

part of the M.Pharm dissertation work of one of the authors of this paper (P.V) using mesophilic strain of a bacterium *Pseudomonas stutzeri* at the Centre for Cellular and Molecular Biology (CCMB, CSIR) Hyderabad, India. Freeze-tolerance of the strain was not enhanced following exposure to heat and high salt but its growth-rate at room temperature was found to be improved.

Concluding remarks

It is obvious from the aforementioned reports, that exposure to mild stress might improve tolerance of bacteria to environmental stressors. The stressors, which are harmful to them at high dose, appear to give them some advantages at low dose. The observations made by the investigators affirm and corroborate the aphorism of the 19th century German philosopher Friedrich Nietzsche “What does not kill me makes me stronger”. Looking from a broader point of view, we find that there are several types of stressors or adverse conditions which are harmful to the living cells in high dose but beneficial in smaller dose. The differential response of living cells or organisms (low dose stimulation, high dose inhibition) to various physical agents (temperature, pressure, radiation) and chemical substances (acid, alkali, salt, some toxicants) is known as hormesis. At present, it is beginning to be understood by the investigators in the area of pharmacology, toxicology and medicine [8,9].. Significant addition to the present state of knowledge is expected during the next few decades.

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Anthelmintic activity of hydroalcoholic extract of fruits of *Solanum seaforthianum* and *Solanum erianthum*

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Abstract:

Genus *Solanum* possesses wide range of activities in traditional system. For our present study, we have explored fruits of *Solanum seaforthianum* and *Solanum erianthum* for their phytochemical constituents and investigated for anthelmintic effect. Phytochemical constituents were analysed using preliminary tests and FTIR. The anthelmintic activity of hydroalcoholic extracts of both the fruits were evaluated against earthworm *Pheretima posthuma*. Phytochemical investigations revealed the presence of alkaloid, glycosides, phenols, saponins, tannins, terpenoids and flavonoids. The study revealed that the hydroalcoholic extracts of the fruits of the plants showed significant anthelmintic activity in a dose dependent manner leading to spontaneous immobility / or death of earthworms.

Keywords: *Solanum seaforthianum*, *Solanum erianthum*, anthelmintic, *Pheretima posthuma*, hydroalcoholic extracts.

Introduction :

Human population in developing nations as well as live stocks all over the world are majorly affected by gastro intestinal parasites [1]. Helminthiasis is the most common infections in humans. These worms first infect the GI tract and later can also seep into other organs, such as the liver, and the toxins released by them can cause serious blood loss in these organs [2]. Helminth infections in domesticated animals produce sub-clinical illnesses and economic losses, making helminths a serious health issue in livestock production. Chronic helminth infection has higher chances of morbidity in both humans and live stocks in comparison to the other parasites [3]. Anthelmintic drugs are expensive, and there long term usage causes severe side effects and may lead to multiple helminth resistance [4]. These elements call for opportunity and environmentally harmless management strategies like herbal natural remedies to be explored in the treatment of Helminth infections. Medicinal plants are being examined for their anthelmintic properties and utilised as anti-parasitic agents all over the world [5].

The plants used in traditional medicinal system in the treatment of infectious disease can be explored for their activity in the crude extracts and analysing their phytoconstituents [6]. Phytochemical constituents particularly tannins have been found to possess anthelmintic properties by impairing different key pathways in the nematodes life cycle [7,8].

From the literature survey, it has been found that *Solanum* species contain steroidal saponins, steroidal alkaloids, terpenes, flavonoids, lignans, sterols, phenolic compounds, coumarins, amongst other compounds [9-11]. Many species belonging to this genus present huge range of pharmacological activities such as cytotoxicity, hepatoprotective, antiulcerogenic, antioxidant, antimicrobial, anthelmintic, etc. In traditional medicine *Solanum seaforthianum* and *Solanum erianthum* have been associated with curing digestive problem, fever, inflammation, headache, leucorrhoea, piles, hemorrhoids, scrofula etc [9,12-16]. For our study, here we have explored the fruits of *Solanum seaforthianum*, *Solanum erianthum* for their phytochemical constitution and anthelmintic property.

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Material and Methods

Collection and identification of fruits :

The fruits of *Solanum seaforthianum* and *Solanum erianthum* were collected in the month of Dec-Feb from Karnataka, India. The authentication was done by Central Ayurveda Research Institute (under Ministry of Ayush, GOI), Bangalore vide authentication ref. No. SMPU/CARI/BNG/2020-21/1304,1305 dated 6/3/2021.

Pre-treatment of raw material:

The fruits were initially washed with plain water, strained and dried under shade for fortnight. The dried fruits along with seeds were then grounded into course powder in a mixer. This powder was further used for extract preparation.

Preparation of hydroalcoholic extract:

Hydroalcoholic solvent mixture was prepared in 3:7 ratio of ethanol: water. Extract was prepared by macerating the grounded powder in solvent for 7 days on electrical shaker. Filtration of mixture was carried out and solvent was removed by evaporation to get dried extract.

Preliminary phytochemical analysis:

Preliminary phytochemical analytical tests such as test for alkaloid, glycosides, phenols, saponins, tannins, terpenoids, flavonoids, carbohydrates, protein, oils and fats for screening the bioactive chemical compounds in the fruits of both the plants were carried out with the hydroalcoholic extracts using the standard procedure as described by Tanaka *et al* [17].

Evaluation of phytochemicals by examining of distinct functional groups included in the extract, which absorb at their own characteristic frequencies, was done using FTIR spectroscopy. The peak values of FTIR were recorded where the functional groups of the compounds were identified in terms of frequency and intensity of absorption [7].

Anthelmintic Activity:

Animal : Pheretima posthuma (Adult Indian earth worms) of about 5-7 cm long were used for the present study.

Standard Drug used : Albendazole suspension (micronized albendazole suspension in the concentration of 10 mg / ml) was used as the standard to compare the test results [18].

Control : Plain distilled water

In vitro anthelmintic activity : All earthworms were acclimatized to lab conditions before experimentation. Animals were divided into five groups: three treatment, one standard and one control. Each group consisted for 6 earthworms/plate [19]. The treatment group earthworms were exposed to three different aqueous concentrations of the extract : 25,50 and 100 mg/ml. The time taken by the worms to be become motionless was noted as paralysis time and to ascertain death, each worm was frequently applied with external stimuli which stimulates or induce movements in the earthworm, if alive [18,20].

The survival time was noted to determine the anthelmintic activity at each concentration. All the results were expressed as a mean \pm standard error of mean of six worms in each group. Micronized Albendazole tablet powder (10mg/ml) was used as a positive control; distilled water was used as control.

Results and Discussion:

Preliminary phytochemical and FTIR analysis Primary phytochemical assays revealed the presence of alkaloid, glycosides, phenols, saponins, tannins, terpenoids, flavonoids, carbohydrates, protein, oils and fats. The IR spectrums of both the extracts are given in Fig .1. The IR spectrum of *Solanum seaforthianum* (a) and *Solanum erianthum* (b); indicates the presence of poly phenols, terpenoids, saponins, alkaloids and sterols.

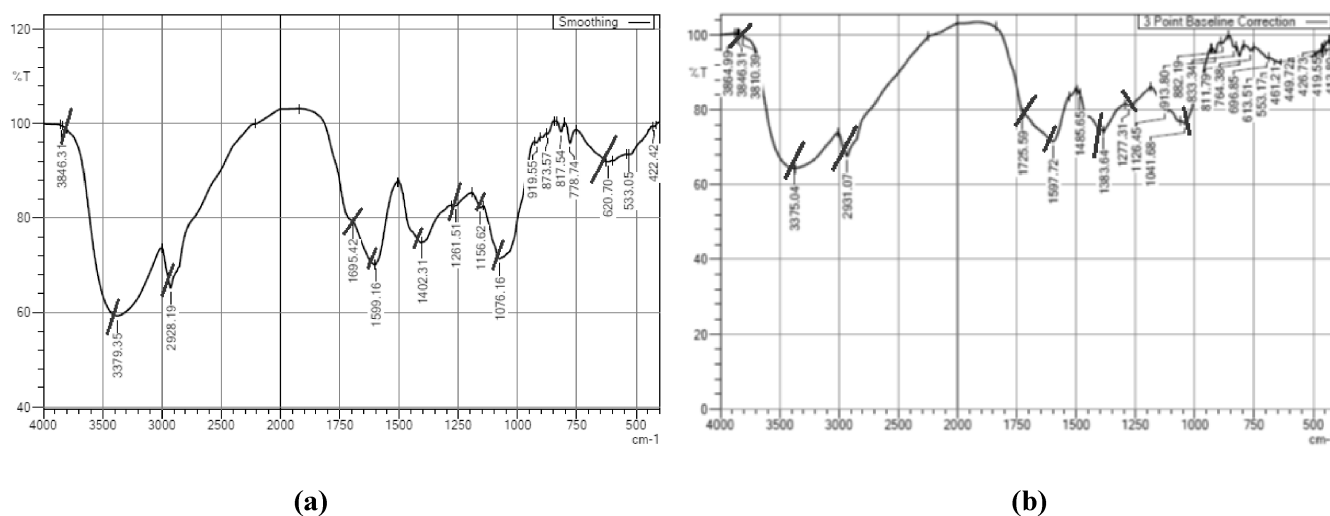


Fig1: IR spectrum of *Solanum seaforthianum* (a) and *Solanum erianthum* (b); showing prominent stretching and bending indicating the presence of O-H, C=O, C-O-C, C-C aliphatic, C=C aromatic stretch. poly phenols, terpenoids, saponins, alkaloids and sterols.

The results in Table 1 and Fig. 2, show that the time taken for paralysis and death of worms after being treated with the substance. The activity at higher concentration (100mg/ml) was comparable with standard drug albendazole. Hydroalcoholic extract showed significant anthelmintic activity against earthworms, comparatively *Solanum erianthum* has shown better activity than *Solanum seaforthianum*.

Table 1: Anthelmintic activity of *Solanum erianthum* and *Solanum seaforthianum*.

Groups	Drug Concentration (mg/ml)	Time taken for paralysis (Min)	Time taken for death (Min)
Normal control	-	-	-
<i>Solanum erianthum</i>	25	42±0.63	64.83±0.75
	50	28.33±0.81	39.83±1.32
	100	18.33±0.81	24.16±0.75
<i>Solanum seaforthianum</i>	25	51.33±0.81	51.83±0.40
	50	38.16±0.40	26.66±1.03
	100	24.66±0.81	19.33±0.47
Albendazole	10	22.33±0.51	20.66±0.51

*The data is expressed as Mean ± SD, n= 6 in each group. One way analysis of variance is followed by post hoc Tukey's Test $p < 0.05$.

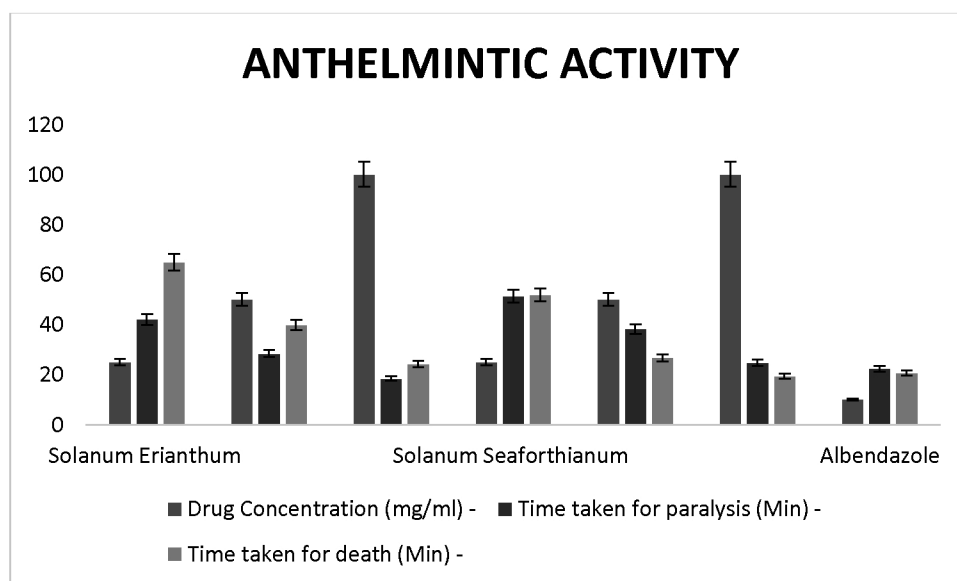


Fig 2: Graphical representation of anthelmintic activity of *Solanum erianthum* and *Solanum seaforthianum*

Albendazole kills the parasites by interfering with microtubular functions such as glucose uptake and glycogen depletion whereas the phytochemical like steroids alters membrane permeability results in pore formation and eventually causes mortality of parasites [21]. Both the fruit extracts demonstrated paralysis as well as death of worms at a time comparable to albendazole at higher concentration. Some phytochemicals such as tannin and phenolic compound also interfere with energy generation in helminth parasites by uncoupling oxidative phosphorylation [22]. Tannins may even lead to parasitic death by binding to free protein in the GI tract of host animal or glycoprotein on the cuticle of the parasite [23]. Phytochemicals such as polyphenols were shown to possess anthelmintic activity against *Nippostrongylus brasiliensis* [24]. Triterpenoids and bitter principals are known to possess anthelmintic activity [25]. Based on these findings, we can say that the tannins, phenols, steroids, terpenoids and flavonoids present in the formulation may be synergistically responsible for the anthelmintic activity of the hydroalcoholic extract.

Conclusion:

The present study assessed the presence of phytochemicals in the crude hydroalcoholic extracts of the fruits of *Solanum seaforthianum*, *Solanum erianthum* using preliminary tests and FTIR. The extract was found to contain tannins, sterols, terpenoids, phenolic components, and glycosides. The extracts showed anthelmintic activity at higher concentration particularly *Solanum erianthum* extracts which showed better activity than albendazole. Future studies to estimate the active components in the extract would be interesting to explore any novel component or mechanism of action of these phytoconstituents along with their toxicity.

Conflict of interest :

The authors declare no conflict of interest in this research article.

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Preparation and topical evaluation of the formulations of *Mikania micrantha* leaves extract

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Abstract :

Mikania micrantha is used to stop external bleeding. It may also be used as analgesic and antiseptic topically. The aim of the study was to evaluate the pharmacological properties of *Mikania micrantha* as a blood clotting agent, analgesic and antiseptic through ointment or gel formulations. The crude drug was obtained, washed thoroughly, dried and size reduced. The crude drug was then extracted with purified water at moderate temperature and the extract was concentrated. The concentrated extract was formulated into an ointment and a gel formulation using suitable excipients. Finally, the formulation was tested on human subjects for evaluation of blood clotting, analgesic and antiseptic properties. The results obtained proved that *Mikania micrantha* ointment and gel formulations had significant blood clotting and wound healing properties. The extract also exhibited antibacterial activity.

Keywords : *Mikania micrantha*, pharmacological properties, gel, ointment; antibacterial effect.

1. Introduction :

Mikania micrantha is a well known weed that grows rapidly and creeps perennially. Due to its fast growth (around 20 cm per day), it is known as the “mile-a-minute” weed. It belongs to the family of Asteraceae and was originally found in Central and South America [1]. A number of species have been identified, but studies have been carried out on few of them. It consists of several constituents like diterpenes, sterols, flavonoids, polyphenols, etc along with several antimicrobial constituents. Research has also been done to evaluate the antibacterial, analgesic, anti-inflammatory and antitumor properties [2]. Further, the essential oils derived from the plant are utilized in cosmetics and pharmaceuticals [3]. The leaves of the plant are commonly called ‘guaco’ and have several biological properties. They have been used in snake bites, treating skin rashes and in wound healing [2, 4].

In the present study, the pharmacological potential of *M. micrantha* was evaluated to stop external bleeding, to be used as analgesic and antiseptic topically and promote wound healing because it is an important natural resource in the traditional medicine.

The objectives of the study are :

- To prepare extracts of the crude drug in water
- To prepare suitable formulations with the extract
- To evaluate the effect of the formulations on wound healing in healthy human volunteers
- To evaluate the antibacterial activity on *Staphylococcus aureus* bacteria in agar media (*in-vitro*)

2. Materials

Fresh *Mikania micrantha* leaves, Carbapol 940, bees wax, hard paraffin, white soft paraffin, cetosteryl alcohol,

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purified water, methyl paraben, propyl paraben, nutrient agar, *Staphylococcus aureus* culture were obtained from Lab India Pvt Ltd..

3. Methods :

3.1 Preparation of aqueous extract of *Micania micrantha* leaves

The leaves were collected and washed thoroughly. Thereafter they were size reduced into small pieces (not >3 cm) and 100 gm of such leaves were added to 500 ml of purified water taken in a 500 ml conical flask. The flask along with its contents was heated at 60°C with regular stirring to facilitate the extraction and kept overnight. The extract was then collected by filtering the mixture with the help of a muslin cloth and stored in the refrigerator at 4°C.

3.2 Evaluation of antibacterial effect on nutrient agar inoculated with *S. aureus* culture

4 gm of nutrient agar was dissolved in 50 ml of purified water by heating at 80°C on a hot plate. The prepared medium was then divided into two parts. In one, 10 ml of the prepared extract and 0.1 ml of *S. aureus* culture were added. In the second one (the Control), only 0.1 ml culture was added with the prepared medium. Then both the media were poured into separate petridishes, allowed to solidify and then incubated at 37 °C in an incubator. Both the petridishes were observed after 24 hours for evaluation of bacterial growth.

3.3 Preparation of ointment and gel formulations with aqueous extracts

Two types of topical formulations (ointment and gel) were prepared with the concentrated extract of *M.micrantha* (Fig. 1).

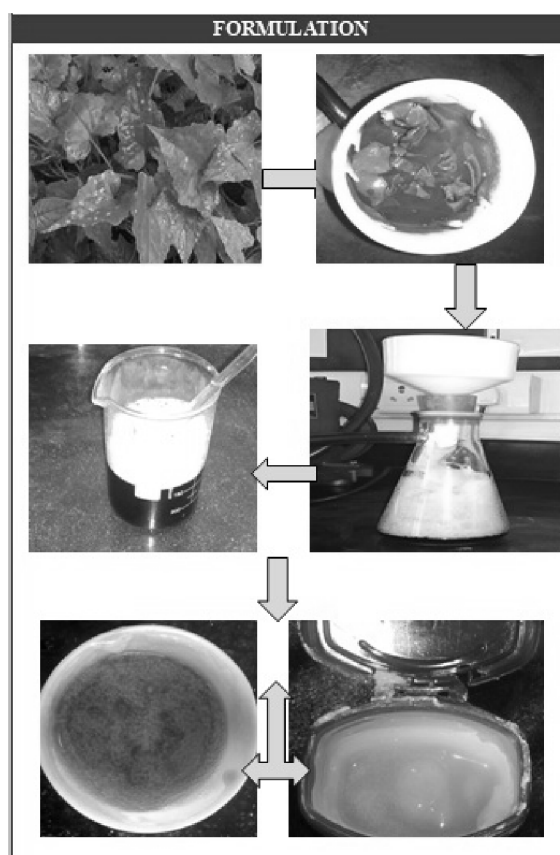


Fig. 1- Preparation of gel and ointment formulations with extract

3.3.1 Preparation of carbopol gel formulations

A solution was prepared with 90 ml of purified water and 10 ml of the concentrated extract. 1g of carbopol 934 was weighed and added to the solution in small amounts and stirred for 1 hour to obtain the gel.

3.3.2 Preparation of ointment formulations

The ointment base was prepared with 0.5 g each of wool fat, cetostearyl alcohol and hard paraffin and 8.5 g of white soft paraffin, according to published literature [5]. Hard paraffin was melted and other ingredients were added to it. Next 10 ml of the concentrated extract of *M. micrantha* were added and stirred continuously until mixed uniformly. The mixture was allowed to cool and solidify.

3.4 Evaluation of wound healing properties of formulations in healthy human volunteers

Five volunteers gave consent for the study. The study was done according to the protocol adopted for blood clotting study. The fingers were pricked with a sanitized needle on one hand and the time to form blood clots was observed. Similarly in the other hand two of the fingers were pricked and ointment and gel formulations were applied. The blood clotting times were observed in each case.

Further both the formulations were applied on a fresh knee wound of one of the volunteers and the wound healing and analgesic properties were evaluated (Fig. 2). The responses from the volunteers were recorded on scale of 1-5 which can be described as below.

Scale	Feedback from volunteers
1	Excellent
2	Very good
3	Good
4	Satisfactory
5	Not satisfactory

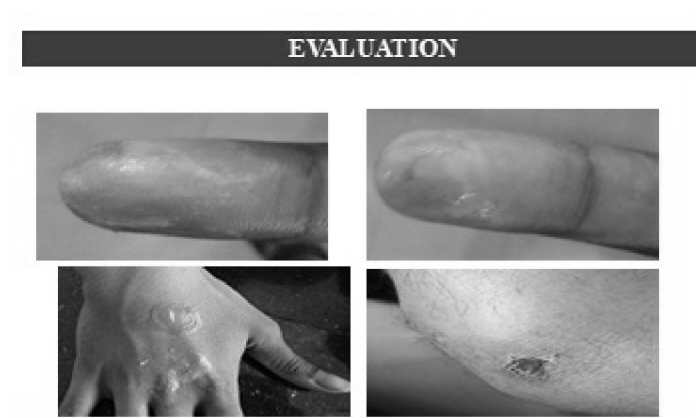


Fig. 2- Evaluation of formulations for skin testing, wound healing and blood clotting

4. Result and discussion

4.1. Antibacterial activity :

The petridish which contained the extract showed no growth of the culture (*S.aureus* suspension) that was added to it whereas the Control petridish showed moderate growth after 24 hours. This showed that the extract

inhibited the growth of *S.aureus* bacteria in agar medium. This may be the reason for better wound healing properties.

4.2. Evaluation of wound healing properties of formulations in healthy human volunteers

The following results were obtained when the formulations containing the extracts were evaluated in volunteers.

Table 1: Responses obtained from volunteers after gel application

Volunteer number	Effect on healthy skin	Blood clotting property (on a scale of 1-5)	Wound healing property (on a scale of 1-5)	Analgesic property (on a scale of 1-5)
V1	Cool sensation with no irritation	3	3	4
V2	Slightly cool with no irritation	4	3	5
V3	Cool sensation with no irritation	3	4	5
V4	Cool sensation with no irritation	4	4	4
V5	Cool and pleasant sensation with no irritation	5	4	5

Table 2: Responses obtained from volunteers after ointment application

Volunteer number	Blood clotting property (on a scale of 1-5)	Wound healing property (on a scale of 1-5)	Analgesic property (on a scale of 1-5)	Comparison between gel and ointment
V1	5	4	3	Gel was better with respect to sensation on skin and analgesic property
V2	4	4	4	Ointment was better with respect to wound healing
V3	3	5	3	Ointment was better with respect to wound healing
V4	4	3	3	Gel was better with respect to sensation on skin and analgesic property
V5	5	5	3	Ointment was better with respect to wound healing

From the results it could be observed that the gel and ointment formulations were both effective in blood clotting and wound healing properties when compared to control. However, there were some differences in the responses for gel and ointment formulations. The gel formulation had a better sensation on skin while the wound healing properties was better for the ointment formulation.

5. Conclusion:

Mikania micrantha has potential benefits. The blood clotting, analgesic, antibacterial and wound healing properties

were evaluated through this study which gave promising results. Formulations containing the extract of the plant can be utilized and marketed effectively for topical use especially for wound healing.

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Microwave assisted grafting of polysaccharide for sustained drug delivery

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Abstract :

Grafted natural polysaccharides have been widely used for design and development of sustained release drug delivery systems. Grafting is an effective tool to tailor make the polymer according to the need of the delivery system. Grafted polymers are synthesized by various methods and characterized by different instrumental analyses. The process of grafting has a profound effect on the characteristics of the grafted product. Apart from that, the choice of monomers, initiators etc also plays an important role towards getting the product of highest grafting efficiency. The swelling, erosion, drug release behavior of the grafted polymer is also dependent on the characteristics of the grafted polymer. In this review article, we present the various methods, types of monomer and initiators used for grafted and its effect on the grafting efficiency. We also present the various grafted polymers that have been utilized for development of sustained release drug delivery systems.

Keywords : Polysaccharides, grafting, swelling, erosion.

1. Introduction

Controlled drug delivery occurs when a polymer, whether synthetic or natural, is carefully coupled with a medication or some other active agents in a way such that the active ingredient is released from that material in a predetermined manner. The active agent's release may be constant over a prolonged period of time, cyclic for a long duration, or triggered by the environmental or other external factors. In any instance, the goal of controlling the delivery of the medication is to provide more effective treatments while reducing the possibility of both underdosing and overdosing [1-2].

Natural polymers are preferred over synthetic polymers for sustained drug delivery because they are more easily accessible, can be chemically modified, economical, renewable, stable, nontoxic, biocompatible, hydrophilic, and biodegradable, as opposed to the synthetic polymers that are expensive and have shown severe toxicity and environmental problems. Polysaccharides are the most abundant natural biopolymers that are gaining popularity as efficient materials in a variety of biomedical sectors, owing to their inherent properties. Polysaccharides have many functional groups, varying physicochemical characteristics, and vital biological functions, making them excellent materials in a variety of pharmaceutical applications such as drug delivery and tissue engineering [3-9].

Natural polysaccharides are extracted from a variety of natural resources like plants, animals, seaweeds and fungus. The various plant polysaccharides include guar gum, tamarind gum, locust bean gum, potato starch, while chitin and chitosan, hyaluronic acid, heparin along with heparan sulfate, chondroitin sulfate, dermatan sulfate, and keratin sulfate belong to animal polysaccharides. The microbial polysaccharides may be acidic like gellan gum or neutral like dextran whereas marine algae are rich in polysaccharides like agar-agar and alginates [10]. However, these natural polysaccharides suffer from several drawbacks such as unpleasant odor, pH-responsive solubility, dull color, and decrease in viscosity after long period of storage, fast degradability at higher temperature, chances of microbial contaminations and uncontrolled rate of hydration [11-12]. To overcome such drawbacks, various types of functionalization of natural polysaccharides are being performed through

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chemical modifications like carbamoylethylation, carboxymethylation, thiolation, cyanoethylation, graft modification, etc.

Grafting has been found to be the most efficient method for changing the properties and structure of natural polysaccharides and microwave radiation is the most effective way of producing sites of free radical on the polymer backbone in the production of graft copolymer. There are two forms of microwave-based grafting method. In the presence of a free radical initiator, the microwave-assisted grafting technique is the most often utilised approach. The microwave-initiated technique is a lesser-known approach in which the free radical initiator is absent despite the presence of the microwave radiation. The microwave-assisted approach has the most potential for the synthesis of graft copolymers since free radicals are created utilising free radical initiators as well as microwave photons, resulting in a considerably greater percentage of efficiency of grafting than the standard method [13].

As for example, Mishra et al. [14] reported that grafting polymethyl methacrylate (PMMA) with xyloglucan (XG) produced a new grafted copolymer with improved thermal stability and shelf life and controlled rate of hydration. Thus, the drawbacks of the pure polysaccharide were removed through grafting. Mishra et al. [15] also performed the grafting of polyacrylonitrile (PAN) onto XG. The thermal analysis data in the case of XG-g-PAN suggested a crystalline behavior in contrast to the amorphous nature of pure polysaccharide thus indicating a decrease in the solubility of the graft copolymer. An improvement in thermal properties was also exhibited by the graft copolymer. In the current review, we will first discuss the grafting of polysaccharides through microwave assisted technique along with their applications in controlled released drug delivery systems.

2. Principles of MW assisted synthesis

The principle of microwave (MW) assisted synthesis is based on the interaction of molecules in a reaction mixture (polymer, initiator, and solvents) under microwave radiation. In the microwave-assisted process, the initiators are added externally and generate free radicals in the reaction mixture. This free radical generally initiates grafting by the free radical polymerization process in the constant microwave dielectric heating [16].

3. MW assisted grafting of polysaccharides

The microwave-assisted grafting technique is one of the significant grafting methods that can be used for the improvement of the polysaccharide properties. An initiator is introduced to the reaction externally to enhance the reaction rate. These external initiators produce free radicals and free radical sites on the preformed polymer backbone that initiate grafting in the presence of microwave radiation [17]. Also, grafting in the aqueous mixture improves the capability to transform microwave energy to heating energy and the heating energy reaches into the core of the reaction mixture rapidly [18]. This results in the rapid interaction of the molecules in the mixture and facilitates consistent heating with high heating energy. Thus, MW-assisted grafting takes a shorter synthesis time [19].

3.1. Synthesis and mechanism of polysaccharides grafting

MW-assisted grafting of polysaccharides is carried out under microwave radiation in the presence of free-radical initiators and/or catalysts, as well as often crosslinkers. These initiators are introduced into the reaction to accelerate the reaction rate and generate primary free radicals. Under the microwaves, the initiators react with the molecules of the mixture. The initiator produces primary free radical ions in the reaction mixture. These primary free radicals create radical ion sites on the polysaccharide and act as macroinitiators for the monomer. Subsequently, the monomer molecules are linked to the radical ion sites of polysaccharides by their radical ion sites, which are created by free radical ions. Through the propagation and termination steps, resulting in a graft copolymer. Thus, free radicals are initiated and carried out grafting by free-radical polymerization in the presence of microwave radiation. In the MW-assisted method of reaction, copolymerization is preferred over homopolymerization, and the yield amount of grafting material becomes higher. Polysaccharide grafting processes under the influence of microwaves become more prolific and selective when done in the presence of initiators.

These reactions of grafting have been extensively explored for the production of modified polysaccharides for a variety of applications [20].

3.2. Factors affecting grafting of polysaccharides

Various factors, including the concentration of polysaccharide, monomer, initiator, as well as exposure time (MW), influence on grafting of polysaccharides in microwave-assisted methods to achieve the optimum grafting efficiency.

3.2.1. Effect of polysaccharide concentration

The concentration of the polysaccharide is important as grafting includes the linking up of a monomer to a pre-formed polysaccharide backbone. Grafting increases with increased polysaccharide concentration up to the optimum value while other factors remain constant. The reason is that more macroradicals are available in concentration for grafting. Beyond the optimum value, grafting (%grafting efficiency or %E) declines, perhaps owing to an increased viscosity which hinders the process in the reaction medium. % Grafting (% G) is decreased continuously as the polysaccharide increases as well as the viscosity of the polysaccharide also increases. This hinders the motion of initiator molecules, thus reducing the possibility of grafting. Additionally, a high polysaccharide concentration can generate more polymeric macroradicals, which are combined to terminate the reaction. As a result, grafting parameters are declining. Table 1 represents the research work on the effect of polysaccharide concentration on grafting.

Table 1: Effect of Polysaccharide Concentration on the Grafting of polysaccharides

SL. No.	Grafted Copolymer	Polysaccharide	Monomer	Polysaccharide concentration	Grafting	References
1.	Poly aniline (PANI)-g-gum acacia (GA)	Gum acacia (GA)	Aniline (ANI)	Increased	%E increased then decreased & %G decreased	21
2.	N, N'-dimethyl acrylamide (DMAAm)-g-Sodium alginate	Sodium alginate	N, N'-dimethyl acrylamide (DMAAm)	Increased	%E & %G decreased	22
3.	Xanthan gum -g- acrylic acid	Xanthan gum	acrylic acid	Increased	%E increased & %G decreased	23
4.	Poly(acrylamide)-g-carboxymethyl xanthan gum	carboxymethyl xanthan gum	acrylamide	Increased	%E & %G increased then decreased	24

3.2.2. Effect of monomer concentration

The concentration of the monomer also impacts grafting as the optimum monomer concentration is required to react with the polysaccharide backbone. Under constant concentrations of polysaccharides, initiator, and exposure time, grafting is increased with the increase of monomer concentration. The rise in grafting might be attributed to the creation of more monomer radical ions. This would also result in more grafting sites and more monomers available for grafting. Grafting decreases as the monomer concentration increases after the optimum value. This is likely owing to the greater homopolymer of monomer synthesis. Table 2 represents the research work on the effect of monomer concentration on grafting.

Table 2: Effect of Monomer Concentration on the grafting of polysaccharides

SL. No.	Grafted Copolymer	Polysaccharide	Monomer	Polysaccharide concentration	Grafting	References
1.	Poly aniline (PANI)-g-gum acacia (GA)	Gum acacia (GA)	Aniline (ANI)	Increased %G increased	%E increased then decreased &	21
2.	N, N'-dimethyl acrylamide (DMAAm)-g- sodium alginate (NaAlg-graft-PDMAAm)	Sodium alginate (NaAlg)	N, N'-dimethyl acrylamide (DMAAm)	Increased	%E & %G increased then decreased	22
3.	Acrylic acid -g- Artemisia seed gum	Artemisia seed gum	Acrylic acid	Increased	%E & %G increased then decreased	25
4.	Polyacrylamide -g- Guar Gum	Guar Gum	Acrylamide	Increased	%G increased then decreased	26
5.	Potato Starch -g- poly(acrylamide)	Potato Starch	Acrylamide	Increased	%E decreased & %G increased	27
6.	Xyloglucan-g- acrylonitrile (AN)	Xyloglucan	Acrylonitrile (AN)	Increased decreased	%E & %G increased then	28
7.	Methyl methacrylate-.g-acetylated <i>Saccharum spontaneum</i> L	Acetylated <i>Saccharum spontaneum</i> L. fiber	Methyl methacrylate	Increased	%E & %G increased then decreased	29
8.	Polyacrylamide- g- carboxymethyl guar gum(CMG-g-PAM)	Carboxymethyl guar gum	Acrylamide	Increased	%E increased then decreased	30

3.2.3. Effect of initiator

Apart from the radiation technique, all chemical grafting reactions require an initiator, and its concentration needs to be considered. Grafting is increased with an increase of initiator while concentrations of polysaccharide and monomer are constant. It's possible that at this concentration range, the more radical moieties activate the backbone of polysaccharides and simultaneously produce the monomer radical, followed by monomers being grafted onto the polysaccharide backbone. In some cases, %E decreases, which is explained by noting that an increase in the amount of initiator can cause an increase in the monomer homopolymerization. Table 3 represents the research work on the effect of initiator concentration on grafting.

Table 3: Effect of Initiator Concentration on the grafting of polysaccharides

SL. No.	Grafted Copolymer	Polysaccharide	Initiator	Initiator concentration	Grafting	References
1.	Poly aniline (PANI)-g - gum acacia (GA)	Gum acacia (GA)	Ammonium peroxydisulfate (APS)	Increased	%E & %G increased	21
2.	N, N'-dimethyl acrylamide (DMAAm) -g- sodium alginate (NaAlg-graft-PDMAAm)	Sodium alginate (NaAlg)	Azobisisobutyronitrile (AIBN)	Increased	%E & %G increased then decreased	22
3.	Acrylic acid -g- Artemisia seed gum	Artemisia seed gum	Ammonium peroxydisulfate (APS)	Increased	%E decreased & %G increased	25
4.	Polyacrylamide -g- Guar Gum	Guar Gum	Potassium persulfate (KPS)	Increased	%G increased then decreased	26
5.	Potato Starch-g-poly(acrylamide)	Potato Starch	Potassium persulfate (KPS)	Increased	%E & %G increased then decreased	27
6.	Xyloglucan-g-PAN	Xyloglucan	CAN (ceric ammonium nitrate/HNO ₃ redox system)	Increased	%E & %G increased then decreased	28
7.	Methyl methacrylate-g- acetylated <i>Saccharum spontaneum</i> L	Acetylated <i>Saccharum spontaneum</i> L. fiber	Ferrous ammonium sulfate-potassium persulfate (FAS-KPS)	Increased	%E & %G increased then decreased	29
8.	Polyacrylamide- g- carboxymethyl guar gum(CMG-g-PAM)	Carboxymethyl guar gum	Potassium persulfate (KPS)	Increased	%E increased then decreased	30
9.	Polyacrylamide- g- gum ghatti	Gum ghatti	Ceric ammonium nitrate (CAN)	Increased	%E & %G increased then decreased	31

3.2.4. Effect of exposure time (MW)

It is clear that to achieve optimal grafting, a significant exposure time is required depending on the polysaccharide. The grafting of polysaccharides improves as the time of exposure increases. This might be due to more microwave energy at longer exposure times. Although on extended exposure, grafting drops are most likely due to graft copolymer breakdown. Table 4 represents the research work on the effect of microwave exposure time on grafting.

Table 4: Effect of Microwave Exposure Time on the Grafting of Polysaccharides

SL. No.	Grafted Copolymer	Polysaccharide	Monomer	MW exposure time	Grafting	References
1.	Poly aniline (PANI) -g- gum acacia (GA)	Gum acacia (GA)	Aniline (ANI)	Increased	%E & %G increased then decreased	21
2.	Acrylic acid -g- Artemisia seed gum	Artemisia seed gum	Acrylic acid	Increased	%E & %G increased then decreased	25
3.	Polyacrylamide -g- Guar Gum	Guar Gum	Acrylamide	Increased	%G increased then decreased	26
4.	Potato Starch-g-poly(acrylamide)	Potato Starch	Acrylamide	Increased	%E & %G increased then decreased	27
5.	Xyloglucan-g-acrylonitrile (AN)	Xyloglucan	Acrylonitrile (AN)	Increased	%E & %G increased	28
6.	Methyl methacrylate-g-acetylated Saccharum spontaneum L.	Acetylated <i>Saccharum spontaneum</i> L. fiber	Methyl methacrylate	Increased	%E & %G increased then decreased	29
7.	Xanthan-g-poly (acrylamide)	xanthan	Acrylamide	Increased	%G increased	32

This observation suggests that the grafting efficiency under microwave irradiation can be controlled to target material with specific properties by controlling the exposure time.

3.3. Removal of homopolymer and purification of grafted copolymer

Grafting reactions and graft copolymerization reactions mostly produce a combination of homopolymer A (homopolymer of the polysaccharide, poly A), homopolymer B (homopolymer of the monomer used), and graft copolymer A-B (grafted product, poly A-B). The methods used for efficient removal of the graft copolymer from the homopolymers are (i) selective precipitation and (ii) extraction [33].

(i) Selective Precipitation

By the addition of a precipitant for poly-A, selective precipitation is normally performed with the purpose of precipitating just one homopolymer, from a solution containing crude reaction product. Because the grafted poly-A-B copolymer may be retained in solution as a dispersed micelle, this separation approach appears to yield successful results. The grafted copolymer can also be coprecipitated with poly-A while leaving poly-B alone in solution. The solubility of the grafted copolymer (poly-A-B) should be sufficiently different from the solubility of poly-B for this purpose.

Ahuja et al. [34] prepared tamarind seed polysaccharide-g-poly(N-vinyl-2-pyrrolidone). The grafted product was precipitated by pouring it into methanol (the homopolymers of monomers formed were soluble in methanol), separated by filtration and finally dried to a constant weight.

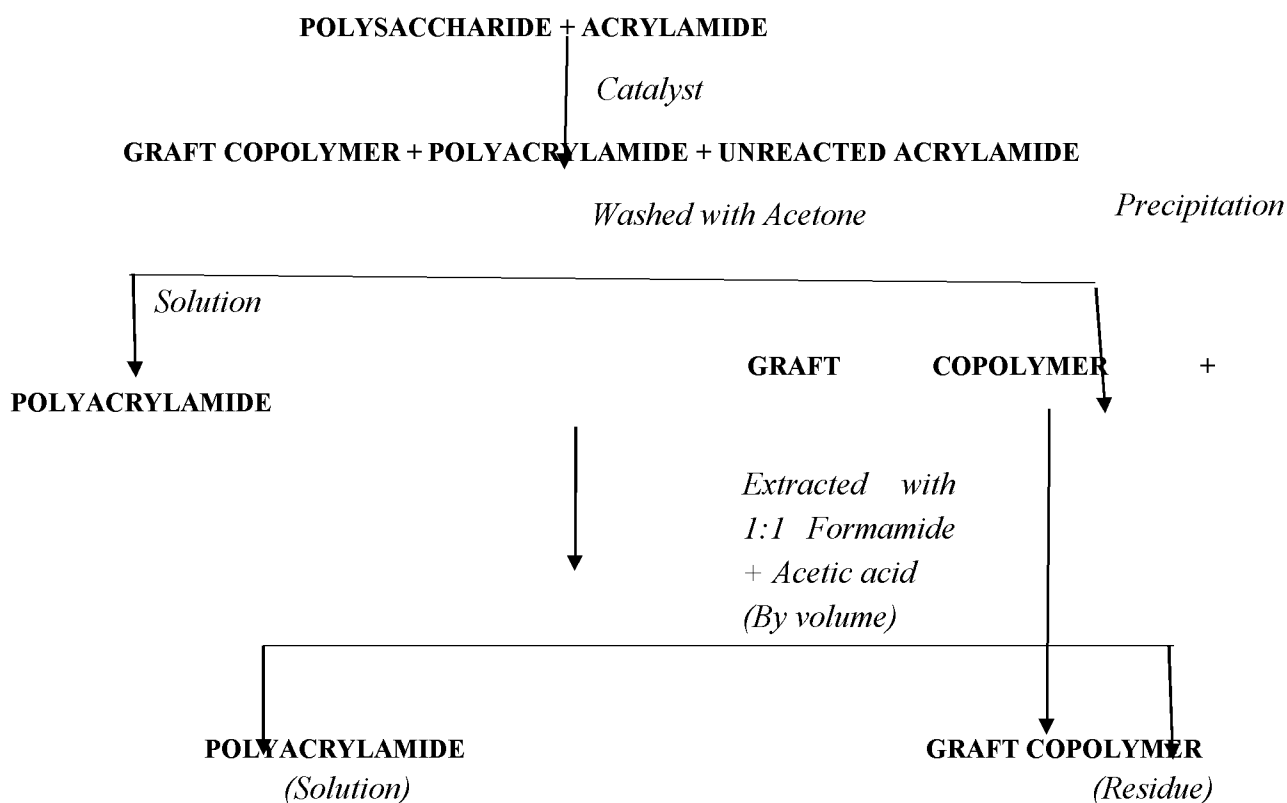
Azmeera et al. [35] developed a biodegradable graft copolymer using dextran (Dx) and 2-acrylamido-2-methyl-

1-propane sulphonic acid (AMPS) by grafting the poly-AMPS chains onto the backbone of dextran. The graft copolymers thus produced were then precipitated with acetone and finally washed almost 10 times by acetone to remove the unreacted AMPS. The resulting graft copolymer was then dried to yield a constant weight at 50°C under vacuum.

(ii) Extraction

The homopolymer trapped in the grafting product can normally be separated by extracting with a suitable solvent during the process of grafting onto films or fibers. This approach is quite straightforward and simple, making it the most frequently utilized, but tedious. It should be noted, however, that if the substrate polymer is left unreacted, then it must be removed first, and finally a significant quantity of homopolymer is extracted. The standard extraction procedure, is insufficient to yield pure grafted copolymer devoid of homopolymers unless both the homopolymers are exposed to a repetitive and alternative extraction.

The extraction of homopolymer is often carried out by solvent extraction using a mixture of solvents, as was done by Sen and Pal when they developed polyacrylamide grafted carboxymethyl tamarind (CMT-g-PAM) [36]. This procedure has been depicted in Scheme 1.



Scheme 1. Purification of graft copolymer

Similarly, Nandi et al. [37] developed polyacrylamide-grafted-tamarind seed gum (PAAm-g-TSG). Acetone was then added to the obtained reaction mixture in a ratio of 2:1 to precipitate the grafted TSG. This was followed by collection of the precipitate by straining and washing with a mixture of methanol-water (4:1) and subsequently with water in order to remove the polyacrylamide and ungrafted acrylamide that were formed. The product was finally dried to a constant weight in a hot air oven at 40°C.

Brockway (1964), on the other hand, made a study on the factors influencing the efficiency of the extraction of homopolymers of methyl methacrylate from the graft copolymers of methyl methacrylate with corn starch (granular) [38]. The efficiency of removing the ungrafted homopolymer in a series of solvents changed in a manner generally paralleling the relative efficiency of solvation of various solvents for the homopolymer. Chloroform and dichloroethane were roughly equally effective in the system of starch/poly methyl methacrylate (PMMA), both being superior to benzene, which in turn is superior to toluene, acetone or methyl ethyl ketone. Soxhlet extraction, while typical for grafted copolymers, was not as successful for the granular starch/PMMA combination as tumbling the hot solvent/polymer mixture in a closed container. It happened most likely owing to insufficient solvent percolation through the swelled up syrupy bulk of graft copolymer in the Soxhlet thimble.

3.4. Characterization of grafted copolymer

3.4.1. Elemental Analysis

The elemental analysis of the pure polysaccharide as well as its grafted copolymer is carried out with the aim of conducting an approximated analysis of three different components: carbon, nitrogen and hydrogen. As mentioned earlier, Azmeera et al. had performed the synthesis and characterization of graft copolymer of dextran (Dx) and 2-acrylamido-2-methylpropane sulphonic acid (AMPS). By elemental analysis it was found that nitrogen was not present in substantial amounts in dextran (Dx) but there was a significant amount of nitrogen in graft copolymers, indicating that grafting of poly 2-acrylamido-2-methyl-1-propane sulphonic acid (PAMPS) chains on the backbone of the polysaccharide was successful.

3.4.2. Intrinsic Viscosity Measurement

The intrinsic viscosity of a polymer is an estimate of the hydrodynamic volume of the polymer in solution, which is, in fact, a function of the polymeric molecular weight, structure, solvent type, and medium temperature. Keeping all the other parameters unchanged, a linear polymer will have a greater hydrodynamic volume and hence a higher intrinsic viscosity than its branched counterpart, for two polymers of nearly identical molecular weight. Furthermore, the longer the branches are along a set of branched polymers, the higher the intrinsic viscosity, and vice versa. Krishnamoorthi et al. (2007) [39] synthesized graft copolymers of dextran (Dx) with polyacrylamide (PAM) by grafting the polyacrylamide chains onto the backbone of dextran. The intrinsic viscosity of all Dx and the graft copolymers were evaluated and it was observed that grafted copolymer exhibited higher inherent viscosity than the pure polysaccharide indicating that it contained longer PAM chains.

3.4.3. FTIR Spectroscopy

Another method of characterization of the grafted copolymers is by performing the FTIR spectroscopy. Mishra et al. (2010) [40], synthesized polyacrylamide grafted starch (St-g-PAM) by the microwave-assisted technique. He recorded the FTIR spectrums of starch and of St-g-PAM between the range 400 to 4000 cm^{-1} and found that grafting took place between the hydroxyl group of starch and the amide group of PAM.

3.4.4 Scanning Electron Microscopy (SEM)

The modification of carboxymethyl tamarind kernel polysaccharide (CMTKP) through grafting was achieved by using acrylonitrile (AN) as the grafting monomer (Ahuja et al., 2014) [41]. The SEM images obtained, confirmed that CMTKP particles were polyhedral shaped and exhibited smooth surface whereas CMTKP-g-poly AN (PAN) exhibited particles that were also polyhedral in shape but with needle-shaped structures which when observed at higher resolution showed CMTKP intertwined with the particles of PAN.

3.4.5 Thermal Analysis

The thermal analysis of the polysaccharide along with its grafted copolymer can provide valuable information about the modified characteristics of the grafted product. Graft copolymer of guar gum with N-vinyl-2-pyrrolidone

was synthesized and characterized by thermal analysis by Srivastava and Behari (2006) [42]. The results concluded that the grafted copolymer was more stable thermally than pure gum.

Guar gum breakdown began at around 200°C. At 100°C, there was a weight loss of roughly 5.94 percent. The rate at which the weight was lost increased as the temperature rose and then gradually declining. As a result, this was a one-step degradation procedure. At 378.2°C, around 70% of pure guar gum deteriorated. Guar gum-g-N-vinyl-2-pyrrolidone on the other hand, began to disintegrate at 200°C. Desorption of water caused a loss in weight by 2.22 percent at 100°C. The grafted copolymer was thermally degraded in two stages, from 180°C to 614.0°C and then from 767.6°C to 956.0°C. Thus, the graft copolymer obtained was thermally more stable than the pure gum.

3.4.6 X-Ray diffractometry

Another method of characterization is by the X-ray diffractometry. As mentioned earlier, Ahuja et al. [34] had synthesized the grafted copolymer of N-vinyl-2-pyrrolidone and tamarind seed polysaccharide (TSP). The crystallinity of the prepared TSP and TSP-g-poly(N-vinyl-2-pyrrolidone) was investigated using X-ray diffractometry (XRD). TSP exhibited an XRD pattern which was typical of the amorphous material and had no sharp peaks whereas the XRD pattern of TSP-g-poly(N-vinyl-2-pyrrolidone) exhibited some degree of crystallinity thus indicating that grafting had taken place.

4. Sustained drug delivery application

Vijan et al., used ceric ammonium nitrate (CAN) as an initiator to formulate acrylamide grafted gellan gum using microwave assisted polymerization [50]. Three distinct process variables like the amount of CAN, the microwave irradiation time and, the amount of acrylamide was used to optimise the synthetic parameters and produce a series of graft copolymers. A higher level of all three factors resulted in greater grafting efficiency (GE percent) of grafted gum. FTIR and ^{13}C NMR were used to confirm the grafting of acrylamide onto gellan gum. DSC was used to successfully evaluate the spontaneity of the grafting process as well as the thermodynamic stability of the grafted gum. The modified gum had a lobule shape and was more heterogenic compared to the native gum, as demonstrated by SEM. The monomer (acrylamide) is hazardous in nature, yet a toxicity investigation in mice demonstrated no morbidity or death during the LD50 trial of AAm-g-GG at a dose of 2000 mg/kg body weight. This grafted gum was used as a rate-controlling polymer in the development of an anti-diabetic drug metformin hydrochloride sustained release tablet. It delayed the release by up to 8 hours, and the release pattern followed the Higuchi square root kinetic model. Fickian diffusion governed the release mechanism. FTIR and XRD tests of the drug and the grafted copolymer revealed no signs of incompatibility. As a result, microwave assisted ceric (IV) mediated graft co-polymerization is a simple, less time consuming, efficient, and reproducible (due to limited production of energy from microwave) technique for the production of graft co-polymer that can be used in the development of sustained release dosage form as a rate controlling polymer.

Kaity et al. investigated the feasibility of using locust bean gum-g-poly (acrylamide) copolymer having buflomedil hydrochloride drug as matrix tablet [51]. This copolymer was produced using a microwave-assisted free radical polymerization process with CAN as the initiator. Since native locust bean gum is non-ionic, it does not exhibit pH-dependent swelling characteristics. However, the grafted co-polymer swelled more at pH 1.2 (221.27%) and at pH 6.8 (281.47%) than the native gum. Because of the introduction of free hydrophilic groups, graft copolymerization of vinyl monomer promoted swelling of the native polysaccharide. The addition of hydrophilic groups was expected to assist the creation of strong hydrogen bonds between the poly (acrylamide) side chains, hence favouring the production of a three-dimensional system with high water retention capacity. After 24 hours, the grafted gum discharged 98.3 % of the drug in simulated gastrointestinal fluids. The biodegradability and non-toxicity (LD50 > 2000 mg/kg) findings were considered to be promising for future clinical application development. The XG-g-poly (acrylamide) tablets outperformed locust bean gum and gellan gum graft copolymer tablets in controlled drug release applications. The potential of graft copolymers based on XG as drug delivery materials was also studied. In the synthesis of graft copolymers, microwave irradiation aids in rapid energy transfer in the bulk of reaction medium, and thus the reaction continues within a very short span of time, even in lack of initiator (Singh, Sethi, Tewari, Srivastava, & Sanghi, 2003).

Anjum and coworkers investigated the potential of microwave-irradiated XG-g-poly (acrylamide) having triamcinolone for colon targeting [52]. Only 3 minutes of 700W microwave irradiation resulted in 61 % grafting of poly (acrylamide) onto XG. Grafting lowered XG swelling in water by 61.29 %. To produce copolymer particles, a triamcinolone-containing copolymer dispersion was mixed with chitosan and calcium chloride (pH4.8). The formation of hydrogel particles was induced by polyelectrolyte complexation between chitosan and anionic graft copolymer, as well as ionotropic gelation among anionic graft copolymer and Ca^{2+} ions. Graft copolymer demonstrated relatively minimal haemolytic activity on human and bovine erythrocytes. The graft copolymer particles delivered a negligible quantity of drug (10%) in acidic media in pH 1.2 within 2 h, but about 98 % in phosphate buffer (pH7.4) after 8 h. In acidic media, graft copolymerization of acrylamide onto XG matrix reduced drug release by 3.5 times. It was expected that drug binding with graft copolymers inhibited swelling and delayed the drug release in acidic media. A greater degree of grafting slowed drug diffusion significantly. This could be due to the effective polymer chain intermingling and less swelling of the polymer matrix.

Kumar and coworkers synthesised XG-g-poly (acrylamide) using microwave irradiation polymerization having ammonium persulphate as the initiator [53]. In contrast, they produced ceric-induced graft copolymer without using MW irradiation technique. The combination of microwave irradiation (100W for 100 sec) and initiator resulted in a considerable increase in grafting yield and efficiency. Microwave-assisted graft copolymerization of acrylamide resulted in a noticeable modification in the shape of the XG particles. Graft copolymer particles were larger in size than non-grafted XG particles. After 16h, non-grafted XG matrix tablets released just 49 % drug in phosphate buffer (pH 6.8). The same, however, was boosted by the graft copolymer tablets. The results revealed that the rate of release was proportional to the percentage of grafting. For the sake of brevity, the tablets composed of copolymer with 190 % grafting released their complete content within 12 hours, but the same with 120 % grafting released just 76 % drug within 16 hours. In comparison, matrix tablets produced with ceric-induced XG-g-poly (acrylamide) copolymer with 62.87 % grafting released only 60% of the drug after 16 h. In a nutshell, the degree of poly (acrylamide) grafting determined the rate of drug release from matrix tablets. A low amount of grafting was found to be advantageous for controlled drug delivery applications. Non-grafted XG matrix tablets swelled significantly despite significant matrix erosion, as reported with graft copolymer tablets. The swelling of copolymer tablets was inversely related to the percent grafting, whereas erosion was directly related to the percent grafting. The drug was released via diffusion, swelling, and matrix erosion. Scheme 4 depicts the drug release mechanism from graft copolymer matrices based on XG.

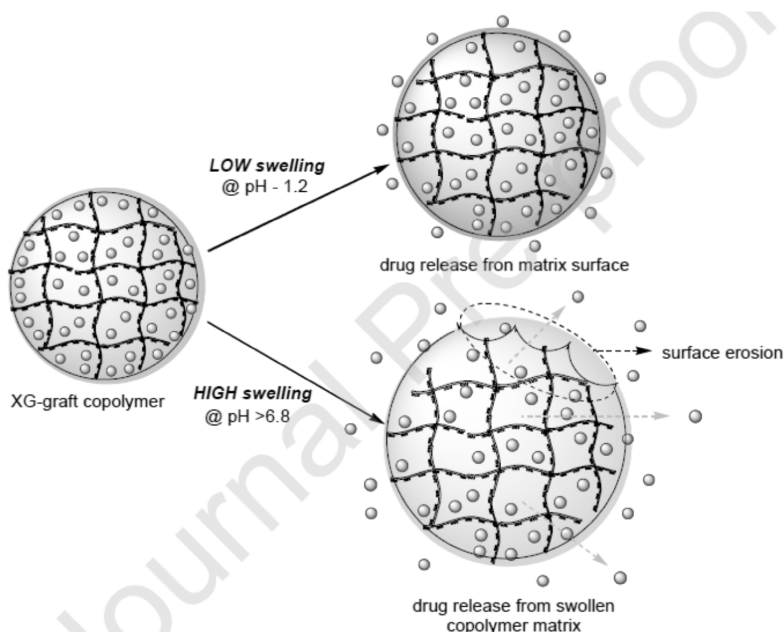


Figure 1.- In- vitro drug release from grafted co-polymer.

Rani and Singh demonstrated the microwave-assisted synthesis of locust bean gum-g-poly(N-vinyl-2-pyrrolidone) with ceric ammonium nitrate as an initiator [54]. Grafting efficiency was 66.3 % using this graft copolymerization technique. The copolymer was efficiently compressed into tablets and investigated for budesonide delivery to the colon. The tablets swelled considerably less (226%) in pH1.2 media than in 7.4 media (275 %). In simulated gastric fluid (pH1.2), native seed gum tablets released more drug (28.51 %) than graft polymer (6.11 %) in 2 h. In the following 3 hours, the drug release rate from unmodified gum tablets (86.71 %) increased than that of graft copolymer tablets (49.11 %) in intestinal fluid (pH7.4). The tablets of unmodified gum and graft copolymer released up to 97.10 % and 82.84 % of their contents in colonic fluid (pH6.8), respectively.

5. Conclusion

Grafting of natural polymers have been immensely used to develop sustained release drug delivery systems. Among the various methods of grafting, microwave assisted grafting seems to be the most used. It is an eco-friendly method which yields product of high grafting efficiency. Proper selection of parameters like initiator, monomers, exposure time has a profound effect on the characteristics of the grafted product, which in turn influences the swelling, erosion and drug release behaviour from the grafted polymer. Optimization of all these variables will yield product of desired quality and characteristics.

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Strategies for delivery of essential oils: a review

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Abstract :

Essential oils are concentrated hydrophobic liquid, composed of mixture of volatile compounds which are produced by the secondary metabolism of aromatic or other variety of plants. They include saturated, unsaturated hydrocarbons, terpenes and their oxygenated derivatives, such as alcohols, aldehydes, esters, ethers, ketones, and oxides phenols. In various field essential oil have attract extensive attention but only 300 out of 3000 essential oils obtained from plant origin have found commercial importance. In this review, we discuss the problems associated with essential oils like high volatility, low water stability, permeability, heat, light, or oxygen sensitivity, bioavailability, poor water solubility, decomposition, and skin irritation; and the strategies to solve these problems are suggested for design of formulation of different nanocarrier systems such as polymer-based nanocarriers, lipid-based nanocarriers and molecular complexes. It is believed that nanoencapsulation of essential oils would improve their therapeutic activity and delivery.

Keywords: Biological activity; cytotoxic; drug delivery; essential oil; nanoencapsulation

Introduction

Use of medicinal plants in healthcare is an ancient as mankind itself and the plant kingdom is the huge source of medication for the humanity. Recognition of the use of medicinal plants by humans is the consequences of countless years of hassle against illnesses [1]. In the report of evolving situation made in the scientific field, keen interests have been given to the therapeutic properties of plants because they exhibit relatively less adverse effects and are safe, eco-friendly and locally available [2].

Plants were strongly believed to have healing power against all the disease in almost all ancient civilizations. Because *Homo sapiens sapiens* is omnivorous, hence take plants or plant parts as principal components of diet for their nutritional content and medicinal value. In drug development, medicinal plants are considered as rich resources of ingredients and, thereby, making them the source for upscale supply of different types of medicines [3]. Some of the drugs obtained from the plant are aspirin, atropine, artemisinin, colchicine, digoxin, ephedrine, morphine, physostigmine, pilocarpine, quinine, quinidine, reserpine, taxol, tubocurarine, vincristine, vinblastine, etc. The medicinal value of plants lies in bioactive phytochemical constituents that produce definite physiological action on the human body. Some of the most important bioactive phytochemical constituents are alkaloids, essential oils, flavonoids, tannins, terpenoids, saponins, phenolic compounds, etc. [4].

This review covers the therapeutic potential of essential oils and problems associated with delivery of essential oils. Possible strategic options to adopt for delivery of essential oils are also described.

Essential oil

Essential oils (EO) are concentrated oily liquid containing volatile chemical derived from plant parts such as seeds (e.g. *Nigella sativa*, *Anethum graveolens*), fruits (e.g. citrus fruits), fruits peel (*Citrus japonica*), flowers (e.g., *Lavandula officinalis*, *Halimondendron halodendron*), roots (e.g., *Ballota nigra*, *Valeriana jatamansi*, and

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Zingiber officinale), rhizome (e.g., *Zingiber officinale*), buds, twigs, leaves (e.g., *Artemisia monosperma*, *Artemisia douglasiana*, *Pimenta dioica*, and *Eucalyptus citriodora*) wood or bark (*Cordia trichotoma*, *Cinnamomum cassia*) [4]. In the sixteenth century, Swiss reformer of medicine Paracelsus von Hohenheim coined the term “essential oil”, derived from the term *Quinta Essentia*. Essential oils are also termed as volatile or ethereal oils. They are widely being proven as sources of natural antimicrobial compounds as they are mainly composed of monoterpenes and phenylpropenes with known microstatic and microbicidal effects [5]. Besides antimicrobial properties EOs or their components have been shown to exhibit antiviral, antimycotic, antiparasitic, antioxidant, cytotoxic, anti-inflammatory and insecticidal properties [6]. EOs are fat soluble and the molecules are small in size so that they are able to pass across the membranes or the skin and reach the systemic circulation before being entering the microcirculation [5-9].

There are about 3000 different plant species containing EOs that have been reported, out of which only 300 of them are economically important. EOs are used in the fragrance, food, pharmaceutical, agricultural, and sanitary industries. They are formed through a schizolysigenous process in cluster gland cells and accumulated in secretory cavities, cells, epidermic cells, glandular trichomes of plant organs [6]. EOs can be extracted by several methods which involve utility of microwaves or liquid carbon dioxide, and predominantly low- or high-pressure distillation engaging heated water or hot steam. Owing to their bactericidal and fungicidal properties, pharmaceutical and food uses are more widespread as another substitute to synthetic products. In such cases, extracted by steam distillation or by expression is preferred and for perfume uses, extraction with lipophilic solvents or supercritical carbon dioxide is chosen. Thus, the essential oil products vary not only in their chemical profiles or molecules numbers but also in the molecules of stereochemical types extracted, in accord with the type of extraction. Depending on climate, soil composition, age, plant organ, assemblage time and vegetative cycle stage, the quality, quantity and composition of the extract vary considerably [5].

Components of Essential Oils

All the essential oils individually have more than a hundred components and their components vary depending on the oil in question. Yet, the commonly found active compounds in essential oils are categorized into two chemical groups, namely terpenoids (monoterpenoids and sesquiterpenoids) and phenylpropanoids. Their precursors of the primary metabolism are different and are synthesized through separate metabolic pathways. Essential oils are mainly made up of hydrocarbon molecules and are further classified as terpenes, alcohols, phenols, aldehydes, ketones and esters, etc. They also possess other components such as oxygenated compounds, monoterpene alcohols, sesquiterpene alcohols, lactones, coumarins, ethers, oxides, etc. Some of compounds found in essential oils are discussed below:

Terpenoids: Majority of essential oil containing plants possess terpenes and terpenoids as the primary constituents. Again, terpenoids containing plants, mostly belong to the monoterpene and sesquiterpene families.

Monoterpene / Monoterpenoid: These compounds are found in nearly all essential oils and their structure consists of 10 numbers of carbon atoms with at least one double bond. Some examples of monoterpenes and monoterpenoids are limonene (present in citrus fruits), geraniol, terpineol (present in lilacs), myrcene (present in hops), pinene (present in pine trees) or linalool (present in lavender).

Sesquiterpenes and Oxygenated Compounds: Sesquiterpenes group contains 15 numbers of carbon atoms with the molecular formula $C_{15}H_{24}$ and have multiplex pharmacological actions, for example chamazulene, which is found in German chamomile. The most common type of functional group found in essential oils is the oxygenated group and they contribute their own unique potential health benefits.

Esters: Esters are also very common and are present in a large number of essential oils. They are fruity in nature and have calming and relaxing effect along with the therapeutic effects, like sedative and antispasmodic. Some ester compounds also possess anti-fungal and anti-microbial effect. One of the beneficial ester compounds present in the essential oil is linalyl acetate, which is found in plants like bergamot, Clary sage, lavender as well as petit grain with geraniol acetate found in sweet marjoram.

Ketones: Essential oils that contain Ketone compounds are found in plants like Clary, sage, Hyssop, Idaho, Tansy, Rosemary and Western red cedar. Ketones obtained from such plant show therapeutic action, such as mucolytic and Neuro-toxic. They can stimulate regeneration of cell, promote the formation of tissue, and can liquefy mucous. They can be used in conditions such as dry asthma, flu, colds, and dry cough and are largely found in oils which are used for the upper respiratory system dysfunction [10].

Major biological activities of essential oil

The major biological activities of essential oil are shown in Figure 1.

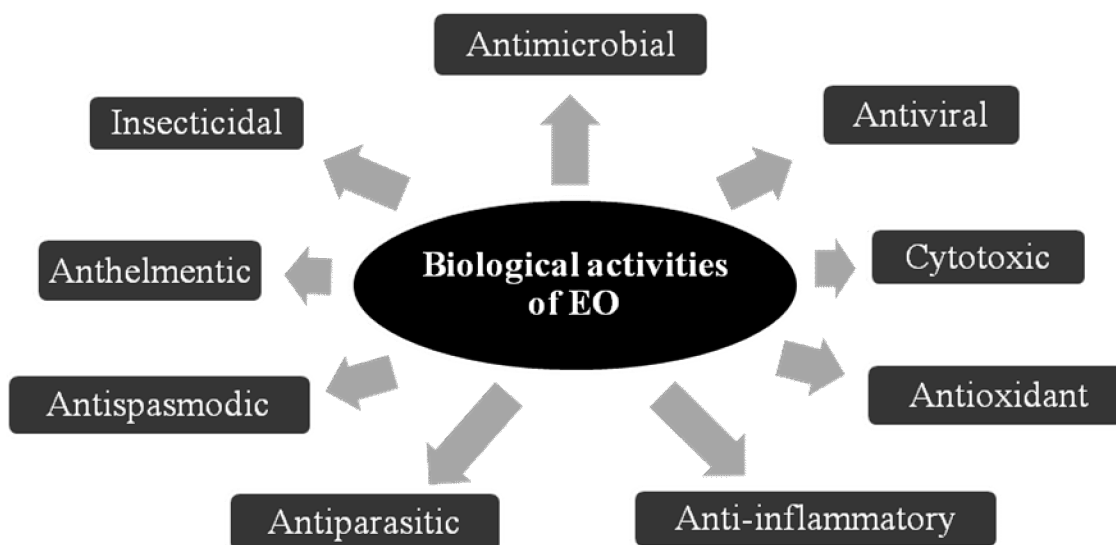


Figure 1: Major biological activities of essential oil

Problems in delivery of Essential oils

The use of EOs in their free form reduces their effectiveness because they easily get volatilized and decomposed when exposed to oxygen, light, humidity, heat or irradiation [11]. Essential oils are unstable and possess poor water solubility. The components of EOs that belong to the same chemical group are structurally similar which results easy inter conversion of the component, enzymatically or chemically triggering oxidation, isomerization, cyclization, or dehydrogenation reactions [12]. These changes can occur during handling of the oil or during distillation, processing and storage of the plant material. Again, some oil, like bergamot oil can cause photosensitization reaction and can even induce malignant change.

Sometimes aromatherapy can cause skin irritation, especially if the oils are concentrated. Even applying the concentrated oil topically, in excess amount to broken or on the large surface of the skin can cause serious side effects as they undergo systemic absorption. Storing EO for long duration of time may result change in the organoleptic characteristics along with a change in viscosity and oxidation of terpenoids compounds results hypersensitivity reaction like allergic contact dermatitis [12].

Strategies suggested

A possible strategy to solve the problems related to stability, solubility, bioavailability of oil would be through the preparation of their micro or nano formulation, in order to increase protection against instability, decomposition and to improve therapeutic efficacy. To preserve oil through encapsulation various colloidal systems can be used such as nanoemulsions, liposomes, microemulsion and microcapsules, etc. The proposed strategies to overcome the shortcoming of essential oil delivery are given in Figure 2.

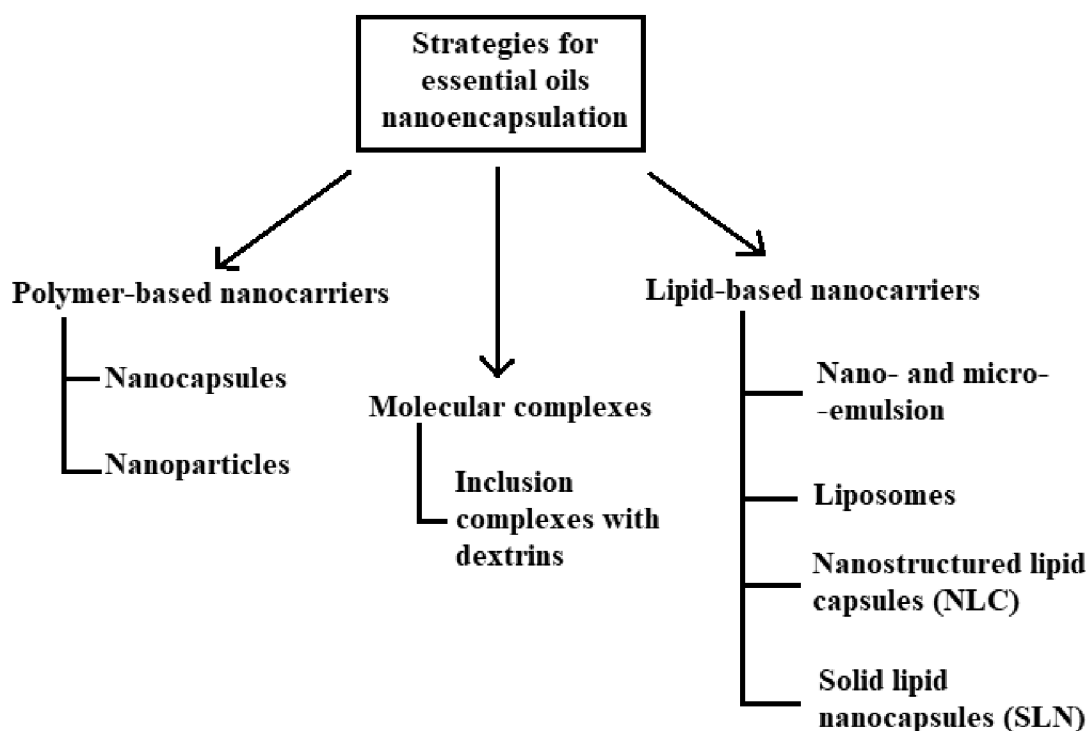


Figure 2: Strategies involved in the delivery of essential oil

Polymer-based nanocarriers

Nanocapsules

Nanocapsules are vesicular systems consisting of nanoscale shell made from a nontoxic polymer and a space/core which can be aqueous or oily where the desired substance is confined. The active ingredient incorporated in the core can be solid or liquid. If the active substance is lipophilic then it may get solubilised in the core cavity or may get adsorbed on the polymer shell depending on its solubility [13]. Nanocapsules are sub-microscopic colloidal drug carrier systems and its sizes range from 5 to 1000 nm, but usually the accepted range is in between 100-500 nm [14]. They can be prepared by various methods, namely, nanoprecipitation, emulsion/solvent diffusion, double emulsification polymer coating, salting out, dialysis, solvent evaporation, interfacial polymerization, and supercritical fluid technology. They provide good shielding environment to peptides, hormones, proteins, enzymes, drugs, metabolites, or molecules against biological and chemical degradation; they can also delay the release of active ingredients and possess site specificity, therefore they have attracted great interest in drug delivery system [14]. The advantages of nanocapsules include, higher encapsulation efficiency, specific absorption mechanism across the GIT, sustained release, biocompatibility, biodegradability, membrane efflux transporter inhibition, targeting potential and oral deliver ability [15]. Considering these advantages, these systems can actually provide a novel approach for delivering essential oil and overcoming its limitations. There is a report on nanocapsules as a system for carrier of vitamin E, prepared by the nanoprecipitation method for laboratory scale and pilot-scale. This method provided nanocapsules with a mean diameter of 165 and 172 nm, respectively, and with high entrapment efficiency *i.e.*, about 98 % and 97 %, respectively. It has been demonstrated that Chitosan-alginate nanocapsules were developed for encapsulation of essential oil and found that the formulated nanocapsules were hemo-compatible and can be used in biomedical and pharmaceutical field.

Nanoparticles

Nanoparticles are sub-nanosized, solid, colloidal drug delivery systems with particle size ranges from 10 nm to <1000 nm [16,17]. Nanoparticles can be developed into better systems by manipulating the size, surface

characteristics and material employed, which improve therapeutic efficiency and stealth property. Again, this system can deliver the drug in a controlled manner and to the targeted site, which decrease the dose and dosing frequency thereby reduce toxicity and patient non-compliance [17]. Nanoparticles can break the damaged or inflamed tissue and penetration can occur passively or actively. In passive targeting, no ligand is used and targeting is attained when nanoparticles loaded drug reaches the target through the leaky nature of the vessel. However, in active targeting, the carrier system is conjugated to a tissue or cell specific receptor using ligand. For efficient targeted drug delivery, various materials can be used that modify the physiochemical properties which increase their loading capacity, stability and intracellular delivery [16,18]. Nanoparticles can also protect the essential oil from oxidation or evaporation, photo or thermal degradation which helps to extend the shelf life and therapeutic activity of the final product [19]. These features can be considered for overcoming essential oil delivery. Ferreira *et al.*, used Chitosan nanoparticles for encapsulating the EO of *Siparuna guianensis* to prolong its mosquitocidal activity. This study indicates that Chitosan nanoparticles are a suitable system for preserving the properties of EO of *Siparuna guianensis* essential oil in an aqueous medium and protects it from degradation [20]. In another study nanoparticles loaded with eucalyptus or rosemary essential oils were developed and evaluated their wound healing and antimicrobial property; and proved its efficacy and safety in *in vivo* rat model [21].

Molecular complexes

A molecular complex generally attributes to the physical union among a host and a guest molecule. In order to increase solubility and chemical stability of the active ingredient a simple strategy is to physically complex them with another molecule. For EOs the complexes are reported with Cyclodextrins [22].

Inclusion complexes with dextrin

Cyclodextrins (CD) are a family of cyclic oligosaccharides, consisting of five or more glucopyranosyl units joined together by α -1,4-glycosidic bonds. They are also known as cycloamyloses, cyclomaltoses and Schardinger dextrins [23]. They consist of hydrophobic core and hydrophilic exterior, so hydrophobic drug can easily encapsulate into the core of Cyclodextrins with non-covalent interaction which results in change of physical and chemical proportions and thus increase the aqueous solubility and chemical stability of the guest molecule [24]. To prevent evaporation of the volatile compound, allyl isothiocyanate present in 'wasabi', a Japanese spice, an inclusion complex is made with cyclodextrin. In nano delivery, Cyclodextrins facilitate cellular uptake and thereby reduce toxicity. Due to their high stability and nontoxic nature, they have attractive pharmaceutical applications and α forms of Cyclodextrins are widely used as they improve oral bioavailability. Therefore, their complexes with essential oils enhance the water solubility of the EOs; and the chemical modifications in both primary and secondary substituent further improve the solubility and biodegradability with reduced toxicity [25]. The advantages of the CD include protection of the guest molecule against light, oxidation, thermal decomposition, evaporation or sublimation, GIT irritation, drug-drug interactions and elimination of undesired taste/odor, hygroscopicity [26]. These features of the CD carrier system can overcome the limitations related to essential oil delivery. In a study Capelezzo *et al.*, the physical and chemical condition of the α -Cyclodextrins complexation reaction of several types of essential oils along with their release characteristic were investigated and found that encapsulation of EOs using α -cyclodextrin promote their therapeutic uses [27]. Encapsulation of the EO of clove in hydroxypropyl beta cyclodextrin (CEO HP β CD) inclusion complexes in 1:1 molecular ratio using Kneading method was performed in an experiment. The study revealed that this system increased the total phenolic content of free EO as well as total phenolic content of particles and also prolongs the shelf life of the encapsulated EO [28].

Lipid-based nanocarriers

Nano and micro-emulsions

Nanoemulsions (NE) and microemulsions (ME) are transparent, monophasic, optically isotropic colloidal dispersions consists of two immiscible phases, oil and aqueous phase, along with a surfactant and co-surfactant.

The difference between NE and ME are that in case of NE the colloidal dispersion is kinetically stable with droplet sizes less than 100nm while in ME the colloidal dispersion is thermodynamically stable with droplet sizes in the range 10-100 nm [29]. The similarities and dissimilarities between NE and ME are summarized in Table 4.

Table 4: Comparison between Nanoemulsions and Microemulsions

Properties/Parameters	Nanoemulsions	Microemulsions
Physical description	Colloidal dispersion	Colloidal dispersion
Particle size	<100 nm	10 - 100 nm
Polydispersity	Low	Low
Thermodynamic stability	Unstable	Stable
Kinetic stability	Stable	Unstable
Preparation	Low/high energy	Low energy
Composition: surfactant to oil ratio	Moderate	Low
Loading capacity	High	Moderate
Physical appearance	Transparent	Transparent

NE is found to be more efficient for the delivery of essential so, it is described further.

NE can be prepared using two preparation methods viz., low-energy and high-energy emulsification method. The high energy emulsification method includes high-pressure homogenization, ultrasonication and membrane emulsification. The low energy emulsification method includes microfluidization, emulsion inversion point, phase transition and phase-inversion temperature method. The advantages of NE include increased rate of absorption of drug, increased drug loading, enhanced bioavailability, controlled/sustained release of drug and targeted drug delivery. Both lipophilic and lipophobic drugs can be formulated in NE but encapsulating lipophilic drug are found to be more effective, as in this system the droplet size of the lipophilic molecule gets decreases thereby enhances their solubility, stability and subsequently the biological activity. This system is nontoxic, non-irritant because the components used in this system are generally regarded as safe and exclude the requirement of harmful co-solvents, so, they can be used for both parenteral and non-parenteral route. NE can also protect the drugs from oxidation and hydrolysis process. It can be formulated in a variety of formulations such as foams, liquids, sprays and creams. Their long-term stability, ease of preparation (spontaneous emulsification), high encapsulation efficiency, high bioavailability, protection from enzymatic degradation and high solubilisation of drug molecules makes them promising as a drug delivery tool for essential oil [30]. The ingredients required for the formulation of nanoemulsions are given in Table 5 [31,32]. There is a report where nanoemulsions were formulated containing oil of *Cinnamomum zeylanicum* with a droplet diameter of 65 nm using Tween 80 and water by ultrasonic emulsification for 30min which demonstrated bactericidal activity against food-borne pathogen *Bacillus cereus*. The study illustrated that emulsification time, oil-surfactant mixing ratio and surfactant concentration had a significant effect on nanoemulsions droplet diameter and its stability. Another researcher discussed nanosystems with utility in skin delivery and focuses on the composition and characterization of microemulsion and nanoemulsion for topical and transdermal delivery [33]. Similarly, another researcher prepared Plai (*Zingiber cassumunar* Roxb.) nanoemulsions under oil-in-water emulsion system by high pressure homogenization and obtained that an optimal surfactant component in the formulation for fabricating nanoemulsion of Plai with the small droplet size and had an impact on long lasting stability [34].

Liposomes

Liposomes, in the early 1970, are considered among the finest colloidal drug delivery systems that are developed for delivering drugs to a specific site in the body [35]. Liposomes are enclosed spherical vesicles, organized in one or several concentric phospholipidic bilayers with an internal aqueous phase and their diameter ranges from 80 nm to 100 μ m. They are suitable templates for drug delivery as they provide promising drug carriers due to their capability to cutaneous targeting and slow release of the drug [36]. They are also suitable for encapsulating natural compounds like essential oils, which improve its solubility and chemical stability [37]. They prevent the encapsulated bioactive compounds from degradation and increase the solubility of lipophilic compounds. The advantages of liposomal encapsulation include improvement of therapeutic activity and safety, local delivery of medicament at the site of action, controlled and sustained drug delivery, increased bioavailability as their surface can be modified to alter their biodistribution and pharmacokinetics [38]. Liposomes can encapsulate with hydrophilic, hydrophobic and amphiphilic substances. The structural components of liposomes are phospholipids and cholesterol. Phospholipids can be natural and synthetic and the most commonly used phospholipid is lecithin; it is amphipathic. Cholesterol increases the stability of the lipid vesicles by modulating the fluidity of the lipid bilayer [39]. An investigation on the effects of core-wall ratio on the stability and antibacterial activity during storage of the encapsulated Cinnamaldehyde by liposomes was performed and found that liposome-encapsulated cinnamaldehyde might still inhibit bacteria by destroying cell membrane integrity after storage and the persistence was more efficient than that of pure cinnamaldehyde. Therefore, liposomes could improve the stability and long-term antibacterial activity of Cinnamaldehyde. There is a report where nanovesicles were developed by loading essential oils of *Salvia triloba* and *Rosmarinus officinalis*. Liposomes loaded with 100 μ L/mL of EO, were optimized for their size, polydispersity index, ζ -potential, recovery, encapsulation efficiency (EE %), release property and morphology. The prepared liposomes were stable over a one-month period when stored at 4 °C and possessed significant antioxidant, anti-inflammatory and antibacterial activities. The findings suggest that these formulations can decrease the volatility of EOs, optimizes their biological properties and defeat antimicrobial infections. It has been established that phospholipid vesicle from natural soybean would increase the durability of clove essential oil and eugenol which is its main constituent. The study was performed and discovered that liposomes manifested spherical shaped and nanometer coligolamellar vesicles thereby preventing eugenol from deterioration influenced by UV exposure and also conserved the DPPH-scavenging activity of free eugenol and serve as an apt system for encapsulating the components of unstable volatile essential oil.

Nanostructured Lipid capsules

In 1990, Nanostructured Lipid capsules (NLC) were first introduced as a carrier system [40]. They are colloidal drug delivery systems consisting of a fluid lipid phase enclosed in a solid lipid matrix or confined at the surface of solid matrix and the surfactant layer. In these systems, both hydrophilic and lipophilic drugs can be used [41]. The structural arrangement of the lipids provides higher drug loading capacity. The spatial structure of the lipids allows greater drug loading and better stability compared to SLN (Solid Lipid Nanoparticles). These carrier systems can improve stability as well as bioavailability of the active compound and possess excellent biocompatibility [42,43]. NLC is easier to scale-up, sterilize and validate, they also provide controlled and targeted delivery of active constituent [44].

Solid lipid Nanocapsules

Solid Lipid Nanoparticles (SLNs) are nano-dispersion and formulated employing lipids that solidified at room or body temperature. The lipid component may comprise of different varieties of lipid or lipid-like molecules such as triacylglycerols or waxes [45]. SLN can increase the permeation of the active compounds as well as enhance the contact time, which hydrates the skin forming an occlusive barrier, so, these systems are mainly used to load hydrophobic compounds like vitamin A, E and coenzyme Q that increase its stability and reduce its degradation by light and oxygen. The size of these systems varies from 50 nm - 1 μ m and the active compounds get solubilised easily inside or outside the core part [46]. The advantages of these carrier systems

include protection against chemical and physical degradation, sustained/controlled release, improve stability, immobilization of the active compound and suitable for delivery of lipophilic substances [47]. Hence, it serves the purpose of overcoming the problems of EOs delivery.

Conclusions

Essential oils possess important volatile compounds with diverse bioactivities including antimicrobial, antispasmodic, antioxidant, antiviral, anti-inflammatory, anthelmintic, insecticidal, antiparasitic, cytotoxic activity. However, the free form of the EO is prone to physical and chemical decomposition along with poor water solubility, low stability, bioavailability that limits their use in medicines. Therefore, when EOs are delivered in the form of nano-encapsulation provides promising strategies to overcome the shortcoming of EOs. Thus, this will enhance various physiochemical and physiological properties of the EOs and thereby lower their dose, improve safety and therapeutic activity.

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Novel Antibiotics from Marine Sources : A Review

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Abstract :

The antibiotics that brought about revolutionary changes in chemotherapy during the second half of the last century are losing efficacy because of the emergence of antibiotic-resistant strains of microorganisms. Thus, the medical practitioners are left with fewer antibiotics to treat life-threatening infections, and the search for new antibiotics appears to be the need of the hour. Besides making new antibiotics with improved efficacy by chemical synthesis, scientists are also tapping various natural sources to isolate novel antibiotics. Oceans offer a vast area mostly unexplored so far for this purpose. This review highlights the recent developments in the isolation and identification of antibiotics and antibiotic-producing marine microbes.

Keywords : Antibiotics, antibiosis, antibiotic resistance, novel antibiotics, marine-microorganisms.

Introduction

Antibiotics are generally low-molecular-weight chemical compounds with antimicrobial or antibacterial properties that act against microorganisms (other than the producer organisms) at low concentrations [1]. While salvarsan and Sulphur drugs were the harbingers of modern antibiotics, the event that ushered us into the antibiotic era was the serendipitous discovery of 'penicillin' by Sir Alexander Fleming, a Scottish physician and microbiologist in the year 1928 at the St.Mary's Hospital, London, from a fungus *Penicillium notatum* (later in 2011 it was resolved as *P. rubens*.) [2,3]. Subsequently, penicillin became a wonder drug, and its usage rapidly increased during World War II for the clinical management of the wounds of the injured soldiers.

After penicillin, a number of antibiotics were discovered and the period from 1950 to 1960 was regarded as the golden age for antibiotics [4]. Researchers started looking for antibiotics from synthetic as well as natural sources. Between 2000 and 2015, 30 novel antibiotics have been launched among which, 16 are natural or produced from natural derivatives [5]. Naturally produced antibiotics can be derived most frequently either from fungi, (like penicillin) or from various soil bacteria (Streptomycin or Tetracycline) isolated from terrestrial sources [6]. Subsequently, the attention of the researchers was focused on the marine microorganisms as a source of novel antibiotics.

Need for new antibiotics

The new millennium, along with the rapid expansion of the pharmaceutical industry and drug development, has also seen a rise in new diseases. Infectious diseases have become the second leading cause of death worldwide [7]. One of the widespread diseases is microbial infections. The most complex and challenging problem associated with the treatment of microbial infections stems from the emergence of antibiotic resistance in microorganisms. Once upon a time, people worldwide had to die helplessly of tuberculosis, pneumonia, whooping cough, typhoid, and many other bacterial infections. Even after successful surgical operations, patients did not survive because of sepsis. Antibiotics appeared in the field of chemotherapy during the 1940s as a saviour. Common people and scientists started believing that antibiotics, were the magic bullets and thus they were invincible. The euphoria

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did not last long. Within a couple of years, scientists observed that the pathogens susceptible to the antibiotics were begetting antibiotics-defiant progenies. Some strains of bacteria have developed resistance to almost all the generally available agents [8]. One such bacterium is methicillin-resistant *Staphylococcus aureus* (MRSA), which became resistant to most antibiotics used to treat ordinary staph infections. It is also resistant to aminoglycosides, lincosamides, tetracycline, chloramphenicol, and macrolides apart from methicillin. MRSA infections are common in hospitalized patients or people who have been to other health care centres [9]. About 2 out of 100 people carry MRSA. The studies made in 2005 revealed that there were nearly 11,406 *S. aureus*-related deaths, out of which 6,639 were MRSA-related [10]. However, 'pan-resistant' gram-negative bacterial strains are more rapidly emerging in recent years after most pharmaceutical corporations stopped the development of new antibacterial agents. A few of the notable strains of this sort include *Pseudomonas aeruginosa* and, *Acinetobacter baumannii*. These strains are resistant to almost all antimicrobial agents [11].

Antibiotic resistance can be innate or acquired. Mechanism involved in antibiotic resistance include enzymatic transformation, alteration of the molecular target, sequestration of the drug, active efflux from the cell interior, and prevention of the drug entry into the cell [12,13,14]. The accumulation of antibiotic resistance genes occurs through mobile genetic elements like plasmids or transposons or by mutations, which are vertically as well as horizontally transmitted between species [15,16]. This combinatorial genetic strategy resulted in the establishment of multi-drug resistance in bacteria. Multidrug resistance at the molecular level is mainly caused by the enzymatic inactivation of the antibiotics or by alteration of the target site leading to less affinity for the binding of antibiotics or due to failure of the compound uptake caused due to membrane [17,18,19]. The involvement of gene deletion as a mechanism of antibiotic resistance was also demonstrated a few decades back [20].

Generally, different bacteria are resistant to different antibiotics, but when a single bacterium or microorganism is resistant to more than one antibiotic, they are termed multi-drug resistant microorganisms. Multi-drug resistance is due to the accumulation of various resistance-conferring genes resistance on a single DNA segment called a plasmid, whose transfer from one bacterium to another also transmits drug resistance [21].

Niu and Li reported that antimicrobial resistance contributes annually to approximately 700,000 deaths across the world [22]. The 2013 AR threats report stated that at least 2 million people got an antibiotic-resistant infection every year in the U.S., and at least 23,000 died from those infections. These numbers increased rapidly in the later years. A report published in 2019 showed that the number of people affected by antibiotic-resistant infections was more than 2.8 million in the U.S. each year, leading to more than 35,000 deaths. Multidrug-resistant tuberculosis is another rapidly increasing problem, with 490,000 cases out of 558,000 new cases worldwide of tuberculosis with resistance to rifampicin in the year 2017 alone as per studies made by WHO Global tuberculosis report 2018 [23].

The prevailing situation calls for the discovery and development of novel antibiotics with improved efficacy. Most of the antibiotics available now are isolated mainly from soil bacteria. Hence, by searching for antibiotic producers among the soil bacteria, we could expect new penicillin, tetracycline, or aminoglycoside antibiotic. However, pathogenic bacteria are evolving with genetic and biochemical mechanisms to bypass the inhibitory effect of these antibiotics. Thus, novel antibiotics with novel chemical structures and action modes are the hour's need. That is why in the recent past, researchers set their focus on marine sources to design novel antibiotics.

The oceans covering two-thirds of the earth's surface are treasure house with diversified species that produce numerous natural bioactive products, generally called marine biomaterials. These marine biomaterials include biopolymers, bioceramics, marine nanoparticles, marine antibiotics, and many more. Vignesh and his team reported the discovery of 13,000 active biomaterials to date, out of which 3000 had useful therapeutic properties [24]. Extensive uses of these natural products in pharmaceutical industries are well-documented. The branch of biotechnology that deals with the marine biomaterials with the active pharmacological properties is called 'marine pharmacology'; the drugs obtained from marine sources are known as 'marine drugs.' Recently, marine pharmacological works mainly focused on marine microbes and algae [25]. Marine cyanobacteria are one of the promising sources of novel bioactive molecules [26]. Antibiotic resistance genes were spotted in some species of marine sponges, including *Petromica citrina*, which are commonly found on the Brazilian coast [27]. Almost

all the organisms living in oceans are very much diversified and expected to release different biochemical compounds like marine pigments, secondary metabolites, etc., as a part of a defensive mechanism. They are well-adapted to extreme oceanic atmospheres in geysers and hot springs, boiling mudpots, and hydrothermal vents on the deep seafloor. These biochemical compounds released from ocean species also play a vital role in drug discovery and have countless benefits in therapeutics.

The need for Marine Antibiotics

The discovery of new antibiotics is crucial in view of the emerging antibiotic-resistant infections caused by various microorganisms. The toxic nature of certain drugs also limits their use [28,29]. Developing antibiotic resistance in bacteria is in direct correlation with the level of utilization of antibiotics to treat them. So, different antibiotics are required to treat the same infection. For example, previously, penicillin was used to treat an infection by the bacterial strain *Staphylococcus aureus*. Later it was changed from penicillin to methicillin, and now vancomycin is required to treat this infection [30].

Efforts to identify novel antibiotics from terrestrial sources are unlikely to be rewarding for reasons already discussed. The toxicity and untoward effects of some existing antibiotics also limit their application. Thus, the search for new antibiotics appears to be a pressing need for successfully controlling infections. The production of novel antibiotics is either synthetic or natural sources. Modifying the existing antibiotics or antibacterial agents at a molecular level produces synthetic antibiotics. For example, ribosomally synthesized antibacterial peptides are widely existing in the nature as a part of a ubiquitous cellular defense system [31] and are present commonly in all bacteria, plants, animals, and also humans, and they tend to encounter microorganisms [32,33]. Dermaseptins isolated from the South American tree frogs *Phyllomedusa sauvagei* and *P. bicolor* are promising compounds. Despite their enormous advantages, peptides have not yet attained the desired therapeutic significance due to their hemolytic side-effects [34]. Thus, comparatively, natural sources like diverse bacteria or other microbes appear to be more advantageous. Thus, researchers shifted to focus on microorganisms found in new ecological niches like marine sources because oceans are comparatively under-explored habitats than terrestrial environments [35]. Marine microorganisms show tremendous biodiversity and chemical diversity and have a chance of obtaining diversified metabolites that show promising therapeutic properties [36].

Antibiotics from marine microorganisms

Marine organisms are known to produce many beneficial materials with a wide range of compositions that have varied biological properties like antitumor, antimicrobial, anti-inflammatory, and anticancer effects [37]. Thus, following appreciation of the advantages of marine biomaterials, many novel antibiotics were discovered and are still getting discovered from marine sources.

Oceans cover about 71% of the earth's surface, and it holds about 80% of the living organisms [38]. Ocean organisms like sponges, tunicates, mollusks, etc., exhibit unique structural diversity. This uniqueness in structural biodiversity, in turn, leads to chemical diversity and, therefore, a foremost source of natural products that have vast therapeutic properties. Antibiotics are one of those compounds with antimicrobial properties. Antibiotics can be obtained from various marine sources, but marine microorganisms are the best source for compounds with antimicrobial activity. Marine microorganisms like bacteria and fungi show massive antimicrobial properties. Many marine antibiotics have been discovered so far. Nearly 12,322 new compounds have been extracted from marine organisms from 1985 to 2008 [39].

Antibiotics obtained from marine bacteria

Marine bacteria, chiefly present in deep-sea sediments, have shown to produce unique secondary metabolites that have massive bioactive properties and thus, serve as a novel source for antibiotics [40,41,42,43,44]. One of such deep-sea bacteria are members of *Actinomycetes* which act as one of the vital microorganisms in the arena of biotechnology [45]. *Actinomycetes* are one of the best sources to extract bioactive compounds with clinical significance and therapeutic properties [46]. The marine *Actinomycetes* are characteristically diverse

compared to terrestrial *Actinomycetes* [47]. *Actinomycetes* have contributed 45% of all the bioactive metabolites derived from microorganisms because over 10,000 of 23,000 secondary metabolites derived from microorganisms are products of *Actinomycetes* members [48]. Typical members of *Actinomycetes* include *Streptomyces*, *Actinomyces*, *Arthrobacter*, *Corynebacterium*, *Frankia*, *Micromonospora*, *Micrococcus*, and several others [49]. Among these, the genus *Streptomyces* produces a bulky group of secondary metabolites with bioactivity [50]. About 10% of the marine bacterial colonies comprise *Actinomycetes*, which can be isolated from marine sediments [51].

An antibacterial compound, coumarin-6-ol, 3,4 dihydro-4, 4, 5, 7-tetramethyl was extracted from bacteria isolated from marine sediments called *Streptomyces* VITAK1, which showed its activity against drug-resistant bacterial strain methicillin-resistant *Staphylococcus aureus* (MRSA) ATCC 33591 and other Gram-positive and Gram-negative bacterial pathogens [52]. Another strain discovered in India at Parangipettai coastal area, Bay of Bengal (collected by scientists from Periyar University, Salem, Tamil Nadu) named *S.rochei* PM49 produces metabolites having growth-inhibitory effect against MDR and ESBL-producing ATCC strains [53]. *Streptomyces* sp. strain SMS_SU21 is another Indian isolate strain that showed antifungal activity against *C. albicans* ATCC 10231 [54].

Scientists isolated an active antimicrobial lipid compound from marine microorganisms from the Indian Institute of Chemical Biology, Calcutta, which show significantly intense activity against several bacteria and fungi, including multiple drug-resistant strains such as *S. aureus* (strain 23602), *E. coli* (strain DH50) and *Aspergillus niger* (strain MTCC 1344) [55].

Antibiotics obtained from marine fungi

Marine fungi show vast diversity compared to terrestrial fungi. The metabolites released from marine fungi exhibit significant antibacterial, antifungal, and antiviral properties. A fungus that belonging to the Didymosphaeriaceae family, *Paraphaeosphaeria* sp. TR-022 produces novel compounds, like paraphaeosphaeride D (1) and berkleasmin F (2). These compounds, and another known compound called berkleasmin A (3), were found to show anti-MRSA activity [56]. A deep-sea fungus, *Chaetomium* sp. strain NA-S01-R1, produces a new chlorinated azaphilone polyketides, which have antibacterial activity against MRSA [57], and another fungus, *Penicillium* sp. ArCSPf, from the eastern Arabian Sea, produces a pharmacologically active compound, (Z)-Octadec-9-enamide (oleamide), which shows an inhibitory effect against MRSA [58]. Apart from these, A sea mud fungus, *Penicillium* sp. ZZ1283, isolated from Karachi, Pakistan, has synthesized a novel compound, purpuride D (1), that shows antimicrobial activity against several pathogens including MRSA, at MIC values range of 4–14 µg/mL [59]. Another potent bioactive sesterterpenoid compound named terretonin G was isolated from the fungus *Aspergillus* sp. OPMF00272 from poriferan in Japan [60].

• Antibiotics obtained from marine algae

A tropical marine *Cyanobacterium*, *Okeania hirsuta*, was found to produce an effective polyhydroxy macrolide, bastimolide, a compound that exhibited moderate cytotoxic effect and potent antimalarial activity against MDR strains of *P. falciparum* and it is a promising antimalarial drug in the future [61]. *Peyssonnelia* sp. sampled at Solomon Islands, Georgia, USA was the source for the diterpene glycosides, and peyssonosides A”B displayed antimicrobial activity against several test pathogens, along with MRSA at MIC₉₀ of 16.7 ± 0.3 and >50 µg/mL, respectively [62]. Terpenes derived from marine-algae like bromophycolides and their extracts isolated from the Fijian red alga *Callophycus serratus* have significantly inhibited MRSA and vancomycin-resistant *Enterococcus faecium*, with maximal inhibitory concentration (IC₅₀) values of 1.4 µM and 5.8 µM respectively [63].

Conclusion

Considering the increase of multi-drug resistance in most bacteria and microorganisms, researchers need to explore more powerful antibiotics that can show prominent activity against antibiotic-resistant infections. The marine environment has diverse microorganisms that show vast chemical diversity. Marine natural products are abundant and diverse and are a substantial source for developing therapeutics against multi-drug resistant

microorganisms. The action of compounds originating from marine microorganisms is comparable with existing antibiotics and can address the problem of resistance and re-emergence in infectious diseases.

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Prevalence of hypertensive disorder and identifying the associated risk factors among pregnant women attending a teaching hospital in Kolkata.

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Abstract :

Pre-eclampsia is the second most common problem that causes maternal morbidity and complication in low-income countries. It threatens worldwide public health, especially in underdeveloped nations, where it affects 8% of pregnancies. Pre-eclampsia has been associated to socioeconomic, behavioral, nutritional, and associated with demography associated risk factors which were studied in India. There is a death of one pregnant mother every seven minutes from hypertensive diseases during pregnancy. Pre-eclampsia and eclampsia cause most maternal deaths and morbidity. This study's aims to identify population-based etiological associations for pre-eclampsia in a group of Indian women living in Kolkata's urban slums, as well as disorders of increased blood pressure during pregnancy and accompanying maternal consequences. Great progress has been made in development of tests which can predict eclampsia during pregnancy but unfortunately this remains restricted to clinical trials and center around measuring angiogenic profiles, including placental growth factor or newer tests involving metabolomics. This research will investigate the prevalence of risk variables allied with pre-eclampsia and the most prevalent complications linked with pre-eclampsia. It is one of the major causes of maternal death, and according to a report, West Bengal has the high maternal mortality rate, 109 per 100,000 live births. This study has been conducted to identify the risk factors of pre-eclampsia and recommend preventative measures. However, in this study there was no statistically significant relationship with the known hazards of pre-eclampsia a new observation. We have found fewer number of pre-eclampsia cases along with known risk factors could be due to false negative cases

Key words - Pre-eclampsia, hypertension, Maternal Mortality Rate, Multigravida, proteinuria, HELLP Syndrome, Chi Square test, P value, false negative cases, advocacy issues

Introduction

Pre-eclampsia is a prominent cause of maternal illness and death worldwide. A sufficient understanding of an illness adds significantly to its prevention, control, and treatment. Level of knowledge among women who have been pregnant receiving prenatal treatment at a university hospital in Kumasi, Ghana, as well including the characteristics related with adequate understanding. Low awareness of pre-eclampsia exists amongst women who have been pregnant in Ghana. A greater level of education is the most influential element in facilitating adequate pre-eclampsia knowledge. This highlights the need for further efforts to increase women's understanding of PE in order to enhance pregnancy outcomes. Education may be provided by appropriate health education at the ANC, media platforms, or national education program [1]. In India, research was conducted on pre-eclampsia and the social, behavior, dietary, and demographic risk factors that are associated with it. Hypertensive disorder remains the most common cause of maternal mortality. Preventing maternal mortality had been Millennium Development Goal and now part of sustainable development goal.

Pre-eclampsia is also known as toxemia. Pre-eclampsia is new-onset of hypertension and proteinuria during

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pregnancy or after birth. The pregnant women may also have low platelets and renal or liver disorders, may be called (Hemolysis Elevated Liver Enzymes, Low Platelet Count - HELLP Syndrome. Known risk factor of Pre-eclampsia as documented genetic factors, blood vessel problems, autoimmune disorders, twins or multiple births, being over 40 (elderly gravida), being pregnant for the first time, having pre-eclampsia in a previous pregnancy, history of pre-eclampsia within the family, being obese, raised blood pressure history during a previous physical examination, diabetes, disease if kidney, lupus or other autoimmune disorders, and sickle cell disease. Some of the authors have stated previously that pre-eclampsia itself may be autoimmune condition. The known autoimmune condition known to exacerbate during pregnancy are scleroderma, autoimmune thyroid disorders, neonatal lupus and diabetes mellitus type 1 [2-3]

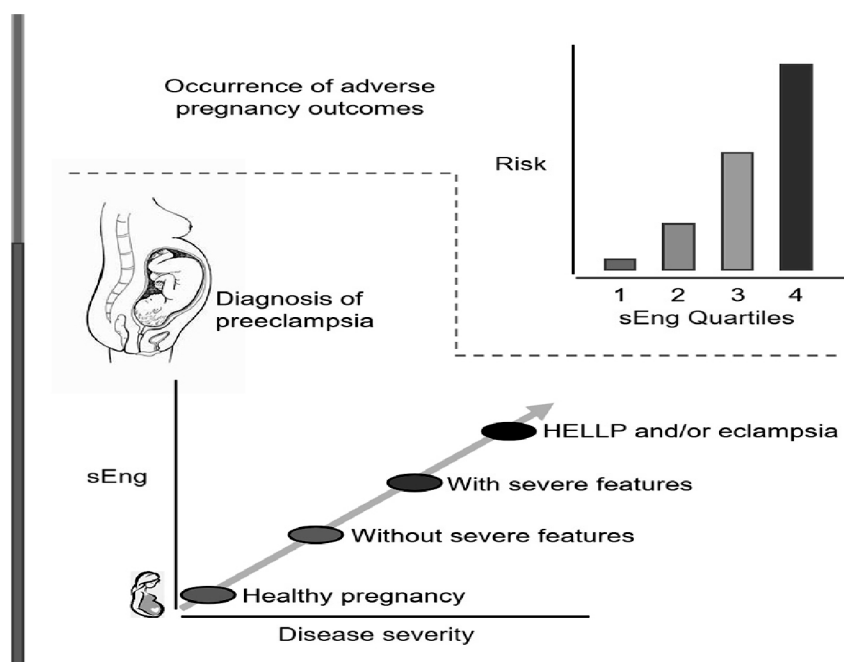


Fig 1: Pathogenesis of pre-eclampsia and pathology leading to complications of hypertension.

Blood pressure is defined as pressure imparted by blood column on the blood vessels. while it is moving through blood vessels. WHO defines hypertension as a blood pressure above 140/90 millimeter of mercury (mm/hg) in an adult measured over 2 different day [1] Gestational hypertension develops during pregnancy when it has attained 20 weeks of gestation without proteinuria or other pre-eclampsia symptoms. About 10-25% of these women may develop pre-eclampsia [3].

Hypertensive disorder of pregnancy- A meta-analysis, the hypertensive prevalence disorders women who are pregnant in India is 1 out of 11 pregnant women. It was shown that the most common forms of hypertension diseases experienced by pregnant women were pre-eclampsia and eclampsia. Pre-eclampsia and eclampsia remain leading features of hypertensive disorder in pregnancy. Evidence from literature has shown among women have been pregnant, 10% of them globally have hypertensive problems. 3–5% of pregnancies have pre-eclampsia. Pre-eclampsia affected 5.4% of the studied population in India. India has not yet met the World Health Organization's Sustainable Development Goals regarding maternal death rates.

Eclampsia has clinical features characterized by one or more spasms in a pregnant woman during delivery or soon after giving birth with elevated blood pressure, sometimes followed by coma. Hypertension complicates 5-10% of pregnancies and, coupled with hemorrhage and heart disease, contributes considerably to maternal morbidity and death. WHO linked 14% of maternal deaths to hypertensive disorders during pregnancy. The American College of Obstetrician and Gynecologist classifies pregnancy-induced hypertension (PIH) into four groups: Gestational hypertension, resting BP 140/90mmHg or greater after 20 weeks; Pre-existing or first-

trimester chronic hypertension; Pre-eclampsia (high BP, oedema, proteinuria)/eclampsia (pre-eclampsia and seizures); Pre-eclampsia with persistent hypertension.

Pregnancy-induced hypertension (PIH) affects 5–8% of all women who have been pregnant globally. Associated hypertensive disorders like pre-eclampsia, eclampsia cause death at birth or around birth. Pre-eclampsia with hypertension and proteinuria affects 5–7% of pregnancies. Premature birth, intrauterine growth retardation, abruptio placentae, and intrauterine death are major causes of PIH, as is death of mothers or within 7 weeks of birth. Data from a cross-sectional survey of 124,385 women age reproductive age group in India's third National Family Health Survey (NFHS-3, 2005-06) can be taken as a reference. 55.6% of responders had pre-eclampsia. Pre-eclampsia was greater in women with twins (95%), those who have terminated pregnancies (95%), severe to moderate anemia, those who smoked (95%), had diabetes (95%), and suffered from asthma (95%). (95 %). a. Pre-eclampsia is prevalent in rural (56.2%) and urban (54%) India. 10 percent of all pregnancies are complicated by hypertensive disorders of pregnancy, which are estimated to cause 40,000 maternal fatalities annually around the globe [2].

If we review the sample registration services (SRS) by Registrar General of India (RGI) for the last 4 data releases. These are 130, 123, 113 and 103. All deaths are calculated in terms of 100,000 live births. The years of estimates are 2014-16, 2015-17, 2016-18 and 2017-19.

The pre-eclampsia incidence is between 3 and 5 percent, according to a research evaluation published in 2020, although its effect is not consistent across demographic groups. certain groups have unusually high incidence and consequence rates. It is seen that elevated blood pressure in women who is pregnant may affect the neonate as he/she is growing may impact cognitive skills, and into adulthood.

According to the Centers for Disease Control and Prevention (CDC), 11.1% of pregnancy-related fatalities in the United States during 2006 and 2007 (the most recent statistics available) were caused by “hypertensive diseases of pregnancy,” such as pre-eclampsia. In 2009, “gestational hypertension,” which includes pre-eclampsia, occurred in 412 births which were born alive per 1,000, or more than 4 percent of all pregnancies, according to CDC data.

In 2015, pregnancy related hypertensive disorders claimed the lives of roughly 42,000 women globally; almost 99 percent of these fatalities occurred in low- and middle-income countries.

According to a FOGSI research, eclampsia causes 24% of maternal mortality in India. Gestational hypertension occurs 5- 10% of pregnancies, although has less severe problems.

Pre-eclampsia/eclampsia remain one of the top three global causes of maternal illness and death. Over 500,000 women die annually from pregnancy-related causes, with 99 % of these deaths occurring in low- and middle-income nations. The incidence is believed to range between 3 and 10 % of pregnancies. In poor nations, eclampsia, maternal complications, and maternal death rates remain high. The maternal mortality rate has been at 1.5%. (2 patients diagnosed with severe pre-eclampsia and 2 with HELLP syndrome) [2] First pregnancy was a protective factor for maternal death ($p=0.008$), while mean transaminase concentration was associated with increased mortality ($p=0.0001$). It is estimated that 8 to 10 % women who have been pregnant in India suffer from pre-eclampsia. In India, 7.8 percent of pregnant women had hypertensive problems, with pre-eclampsia occurring in 5.4% in the group under observation for the study. The maternal mortality ratio (MMR) in India decreased from 113 in 2016-17 to 103 in 2017-18. According to a special bulletin on MMR issued by the Registrar General of India on March 14, 2022, this is the case. The Maternal Mortality Ratio (MMR) in West Bengal, Haryana, Uttarakhand, and Chhattisgarh has increased. At 1968, the death rate of mothers due to pregnancy related issues in a Calcutta district hospital was 4/1000. 42.34 percent of maternal fatalities were due to eclampsia, making it the most important cause of mortality. According to the most recent report of the national Sample Registration system (SRS) statistics, India's Maternal Mortality Ratio (MMR) for the year 2016-18 is 113/100,000 live births, a decrease of 17 points from 2014-16's 130/100,000 live births, however in 2017-19 it has increased to 109. [5]

Significant progress has been made in the development of tests to predict the risk of pre-eclampsia in pregnancy; however, these tests are still only used in clinical trial settings. They focus on measuring angiogenic profiles, such as placental growth factor or more recent tests that involve metabolomics, and they are only available in limited settings. We undertook this study to analyze the most common complications that are linked with pre-eclampsia as well as the most common risk factors that are related with the condition. According to a survey, it is one of the principal determinants that contributes to maternal mortality. As a result, in order to bring down the MMR in West Bengal, this study has been carried out to determine the factors that played a role in the problem and to come up with increasing further preventive measures.

Objectives of the study

- To understand about the most pre-eclampsia linked risk factors in pregnant woman of the reproductive age groups
- To identify most common complications of pre-eclampsia amongst mothers of urban slums in Kolkata
- To study if there is any psychological or drug induced cause behind pre-eclampsia in suffered woman to know about the cause of pre-eclampsia in certain area as there is no particular cause of pre-eclampsia.

Methodology

All the pregnant who were enrolled for the study was from the project areas of reputed development partner CINI in Topisa area of Kolkata. These women has been mobilized as part of CINI's project mandate of ensuring 100% of the pregnant women to have antenatal check up in the government medical college. Total number of population in the project area of CINI has been 28635. The population belonged to the low socioeconomic status.

Total number of women examined was 120.during the study period.

The researcher has used both quantitative method and qualitative method for this study. The period of study in month of middle of May and middle of June. Data was collected using a pre-structured questionnaire, and also in-depth interview was conducted with the beneficiaries. Also, in a few numbers of cases, field visits were undertaken to the beneficiaries' home to make an observation visit.

Data collection tools – Questionnaires, Observation.

Sources of data – checklist, literature review, survey analysis, documents review.

Data analysis – Quantitative data was entered into excel and exported into SPSS IBM release 21.0. Qualitative data was codified. Each of the codified was enter into excel and exported in SPSS in the same version has been explained earlier.

Results

In our study we used the different determinants based on literature review for determining cases of pre-eclampsia in the urban slums of Kolkata. The two most common factors are taken into account that is presence of raised blood pressure and presence of protein in urine has been used to determine pre-eclampsia for prevalence of pre-eclampsia.

As a risk factor of pre-eclampsia, we have used variables – different age group to see which age is more prone to preeclamptic symptoms, income of the family as in many research it is seen that the low income status suffers more from pre-eclampsia, family history as genetics mostly affect pre-eclampsia, obesity, anaemia, gravida, parity ,any autoimmune disease (CVD, renal Other non-gynaecological co-morbidities namely psoriasis, hypothyroidism, hyperthyroidism, diabetes) and other associated cause of hypertension during pregnancy (status of sleep, extra salt intake in diet has been considered to be determinant.

We obtained the data of 120 respondent (pregnant mother) has been taken into the study from survey from government medical college and hospital, gynaecology and obstetrics outpatient department.

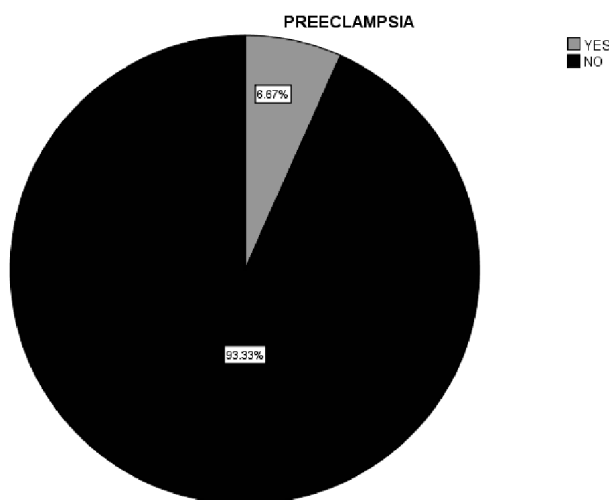


Fig 2 : Incidence of pre-eclampsia (6.7%)

From analysis it is found that 3.33% of total population is affected with pre-eclampsia among the 15-40 years age group women.

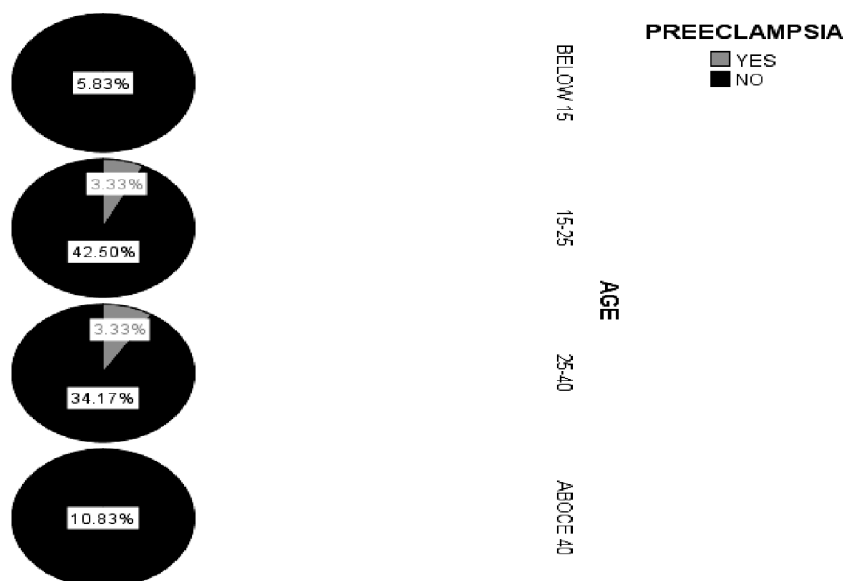


Fig 3 : Pre-eclampsia affected in different age groups

Proteinuria greater than >300 mg/day is considered nephrotic syndrome. No women were found in having these condition. Pregnant mothers have been protein in the range 150-300 mg/day is 10, but blood pressure was elevated in 8, Hence these women was considered pre-eclampsia Proportion of women in this category is 6.7%.

Pregnant women with a positive family history of blood pressure (in excess of 140/80 mm Hg) in the family risk has been 7.4%,

Table 1- Prevalence of pre-eclampsia based on selected co-morbidities

Total number of pregnant mothers is 8 out of 120 (6.7%)					
Age group with hypertension/ total number of women in the age group	Average monthly family income category(Categorized in two groups)	Haemoglobin level in blood	History of prior hypertension Number of beneficiaries/ Total number	Gravida status	Parity Status
Below 15 years 0/7	Prevalence in the group/Sample size	Value of haemoglobin Women with pre-eclampsia/women in the group	No history HTN0/103	Second Gravida Diagnosed/ with PE Total number of women 4/64 (6.3%)	Nulliparous with PE/otal 1/13 (7.7%)
15-24 4 /51 (7.3%)	5000-100008/103 (7.9%)	Below 11gm% 4/84 (6.3%)	History of prior HTN8/17 (47.1%)	3 rd gravida diagnosed with PE/ Total number of 3 rd gravida 4/56(7.1%)	2 nd parity2 nd parity with PE/Total number of women 3/71 (4.2%)
25-39 4/41 (8.9%)	10000-200000/17	Above 11gm- 14.5% 3/22 (7.1%)	Not applicable	NA	3 rd parity or greater 4/36(11.1%)
Greater than 40 0 /13	NA	Above 15 1/ 12 (8.3%) No hemoglobin was tested in 2 people	NA	NA	NA
Chi Square test P value > 0.05 (Within the group)	P value more than 0.05	P value more than 0.05	P value less than 0.05	P value more than 0.05	P value more than 0.05
Age group is not a determinant in this study	Income is not a determinant	Haemoglobin level is not considered a risk factor	Hypertension is a risk factor	Not a risk factor	Not a risk factor

Previous history of auto immune disorders

Table 2 - We had discussed previously in the earlier sections, diagnosed comorbidities and autoimmune disorder possibly linked to pre-eclampsia has been identified. The pre structure questionnaire had these questions related to the autoimmune disorder. The question was simple and had to be answered yes/no. The table below shows the autoimmune disorders which were considered or history of comorbid condition was obtained.

Table 2- prevalence of pre-eclampsia with selected comorbidities

Family History of raised blood pressure	History of obesity	Previous history of miscarriages
Diagnosed as pre-eclampsia/ No family history of BP 8/108 (7.04%)	Diagnosed as pre-eclampsia/ presence of obesity 5/99 (5.1%)	History with PE/Total number of women 3/54 (5.6%)
Diagnosed as pre-eclampsia / Family history of BP0/12	Not diagnosed with pre- eclampsia /non obese 3/21 (14.3%)	No History of PE/ Total number of women5/66 (7.6%)
P more more than 0.05	P value more than 0.05	P value more than 0.05
It is not a risk factor	It is a not a risk factor	Not a risk factor

The results are tabulated as follows

Name of the co-morbid conditions	Yes/No	Proportion of women having the condition	If yes (Action taken)
Cerbro vascular disease	Yes	11.1%	No statistical significance
Any renal disease	Yes	Nil	Nil
Presence of Psoriasis	Yes	7.7%	Not significant
Presence of diagnosed cases of diabetes	No	0%	Not applicable (no cases)
Presence of hypothyroidism	Yes	7.6%	No statistical significance
Presence of hyperthyroidism	No	0%	Not applicable

Hypertension has been associated with increased dietary salt, so the intake of salt in diet plays an important role in occurrence of hypertension during pregnancy. Exact definition of excess salt cannot be quantified, but however based on history it was obtained.

So from the above all the factors we can conclude that the total 6.7 % woman suffer from pre-eclampsia among high risk woman. Most triggering high risk factors found out from survey which effects the cause of pre-eclampsia are age group 15-30 years of age, lower income group mainly o more among obese woman, woman whose gestational week is more than 20 weeks and most important that is the intake of additional salt in diet/ Additionally higher gravida and multiparous carries a higher risk

Discussion

We deduce that 6.7 percent of high-risk women suffer from pre-eclampsia out of sample size of 120. As evidenced from literature review and national health portal of India prevalence of preëclampsia is around 8% to 10% [8] Literature review suggests high risk factors discovered that affect the cause of pre-eclampsia are age group 15-30 years of age, lower income group, more obese women are more prone to pre-eclampsia, woman whose gestational week is greater than 20 weeks, and qualitative assessment the consumption of extra salt is a risk factor. However, in our study there is no statistically significant relation in the known risk factor [1],[3]. This is a new observation. Overall prevalence of lower than national prevalence is lower as stated earlier. There are less known risk factors among the population [9]. Therefore, this can possibly due to false negative cases. There may be an advocacy issue.

Emerging evidence shows that facilitating delivery a little earlier in late preterm pre-eclampsia may protect

against worse maternal outcomes while increasing the likelihood of admission in neonatal unit. Pregnant women in LMICs are among the most vulnerable in the world. Pre-eclampsia is an important cause of morbidity and mortality in mothers and newborns. Community health care workers, particularly women, are an essential component of the health care workforce in many LMICs and are able to provide timely therapy to pre-eclamptic women. In light of restricted resources, every pregnant woman should use pre-eclampsia preventative strategies. In LMICs, monitoring blood pressure and proteinuria is problematic due to cost and lack of experience. Affordable and user-friendly detection technologies are needed. In prosperous countries, pregnancy-induced hypertension with pre-eclampsia and eclampsia continues to be a major problem. Good prenatal care that includes increased awareness and visits may prevent mother and fetal complications. Increasing illiteracy and socioeconomic disadvantage provide the target population for medical treatments and public health initiatives. Preventing maternal and foetal mortality due to pre-eclampsia and eclampsia by identifying cases early by recording blood pressure at each visit, a history of past PE, and diabetes mellitus. Awareness about the early signs of pre-eclampsia and understanding of autoimmune illness are necessary to avoid pre-eclampsia and eclampsia. [1], [3]. We do acknowledge the sample size is quite small to arrive at conclusive evidence. Finally, psoriasis effect on pregnancy has been incompletely characterized. Presence of psoriasis may have other comorbidities may be a confounding variable to be characterized as a risk factor [10]. Some of presence other associated comorbidities that like hypertension, obesity, dyslipidemia, psychiatry disorder and alcohol consumption may coexist. However, women with psoriasis have been associated with pre-eclampsia

Conclusion

Pre-eclampsia is not entirely prevented, however there are a number of measures a pregnant woman may take to mitigate risk factors for high blood pressure which include drinking between 6 and 8 glasses of water every day, avoiding fried or highly processed foods, excluding added salt, avoiding alcohol and caffeine, taking regular exercise under their doctor's guidance, keeping feet elevated a few times per day, resting. Lifestyle interventions may reduce pre-eclampsia, particularly dietary interventions. Lower rates of pre-eclampsia could possibly due to a higher vegetable and plant-based diet.

Ethical Issues

This work has been undertaken in association with CINI, which is in partnership with Department of Health and Family. The project involves tracking of pregnant mothers with hypertension and treating them, therefore prior ethical clearance is implied from CINI's side and Department of Health and Family Welfare. There is also issues non-disclosure statement identifying the beneficiaries and asking non probing questions.

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An observational study among the younger adults in Kolkata regarding their dietary habits and how it is influenced by media

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Abstract :

Media, Advertisements plays a very important role on communication with consumer's especially young people. So, the present online survey was attempted to understand the dietary practices among the young people because of the influence of Media. The objective of the study is to find out association between media influence and dietary practices and to find out the association between media influence and their current Nutritional status. The study was an observational descriptive study based on a set of questionnaires prepared by us. This study included both males and females of a specific age group of 20-25 years. The location of the study was Kolkata, West Bengal with a sample size of 101. It has been seen most of them get highly influenced by sports person followed by celebrities, it might be because they relate the sports celebrities more with fitness. From health point of view there is a huge indulgence in processed foods, ready to eat foods and even on junk foods.

Keywords : Media; young adults; Diet patterns; Health behaviour

Introduction

Young adulthood contributes an important adaptation between adolescence and adulthood and it includes various changes psychologically, physically (Klassen et al., 2018). Due to their life style and peer pressure they largely depend on media for health information as well as they get influenced with promotional gimmick (Dunlop et al., 2016). Media does have productive influence on health but it also promotes unhealthy foods which results into consumption of alcohol, smoking and even low nutritional foods (Freeman et al., 2014). Unhealthy life style during young adulthood can be associated with increased risk with many diseases including atherosclerosis in middle Ages (Spring et al., 2014).

Malnutrition is a serious problem. It is widely seen in United states and nowadays even in other countries. In studies it has been suggested newer generations have more body fat than the previous generation and one of the influential reasons it has been observed is food and beverages promotion on television and other digital media (Buchanan et al., 2018). However in last few years, studies have revealed there is less usage of news from radio and television nowadays the information mostly used are from social media, YouTube.(Goodyear et al., 2021)

A cross sectional studies has been done by authors to visualize the effect of media on diet and physical performance on young adults. On a positive note, the physical fitness has increased at the end of the experiments even healthy modifications of food has been taken place to maintain the healthy wellbeing though this are self-reported measures (Goodyear et al., 2021)

In another literature it was reviewed the effect of marketing on young adults and it has seen five out of ten studies indicates digital marketing has increased their intention to drink alcohol. So, alcohol related marketing posing a detrimental effect on young people drinking behaviour (Maheshwar et al., 2014)

A study was conducted with 1602 advertisement and it has been seen the display of chocolates, cookies were displayed on children's channel more than the 63% adverts of health drinks was displayed on main stream

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channel to target the adults as the cost was high and even adverts of tea and coffee are mostly displayed on mainstream channel. Thus, food advertisers strategically symbolically divided between children and adults. The majority of the advertisements in case of adults and children does not provide authentic information so much more efforts are needed to mention truth about the advertisement and also regulators must encourage display of healthy foods more often (Bala, et al)

In a survey conducted by ASSOCHAM it was reported that Indian adults watch television 14-16 hours a week whereas 26 percent children spend four hours of television per day. Television is a strong medium for promoting the products (M et al., 2018)

Recent analysis has been found in 2018 on young people have 95 % access on smart phones rather than television or radio or newspaper. They prefer YouTube than any other means of medium (Anderson & Jiang, 2018) Some youth thinks reading print news comes into free activity (Anderson & Jiang, 2018) as it becomes difficult to go the valuable source directly and social media helps to communicate, they can express their views so it creates a virtual platform to them (Alkerwi et al., 2015)

Celebrities often endorse commercial foods and beverages so young people often tend to follow them as they get attracted to see the fit body of film actors /actress or sportsperson (Juul & Hemmingsson, 2015) In many studies it has been claimed that media engagement may negatively impact the body image of young people so there comes the health professionals and dietitians to come into the charge and helping them to demolish wrong information which they perceive from the virtual world (Shaikh et al., 2015)

In this research we are focussing to find out their influence of media on their Nutrition awareness to look into their Nutrition status and how their dietary practices are changing due to the influence of media as well

Methodology

The study was an observational descriptive study based on a set of questionnaires prepared by us. The list of questionnaires is furnished below. This study was conducted on a specific age group of 20-25 years. Both male and female were included in this research work. The research work was done in Kolkata, West Bengal. The time duration of the study was from November 2021 to January 2022. The sample size was 101 including male and female.

Questionnaire component

The subtopics are included in the questionnaire focussing on knowledge, attitude and practise of the young adults. The study was done by an online survey where online questionnaire was prepared by Google form. Social media platform was used like Facebook, WhatsApp, LinkedIn. The method of sampling was purposive.

After receiving the filled-up forms, data-based information was statistically analysed using SPSS software (Statistical Package for the Social Sciences) developed by IBM for data management for advanced analytics, multivariate analysis, business intelligence and generating many data outputs.

Results and Discussion

The present study focusses on the assessment of Media influences Dietary Practices on young Adults Kolkata. The study was conducted on 101 respondents included both male and female and it was surveyed online

In odd's ratio according to the table 1 the age is considered to be a risk factor for the BMI. It is an increased occurrence of the event. Many studies have mentioned as well that increased age is one of the risks for malnourishment nowadays (Pal & Pal, n.d.). Even socio-economic scale, alcohol consumption and smoking habits are considered to be the risk factor for malnourishment as the association with many socio demographics scales and behavioural factors are linked with higher BMI are found in previous studies (Rounsefell et al., 2020a)

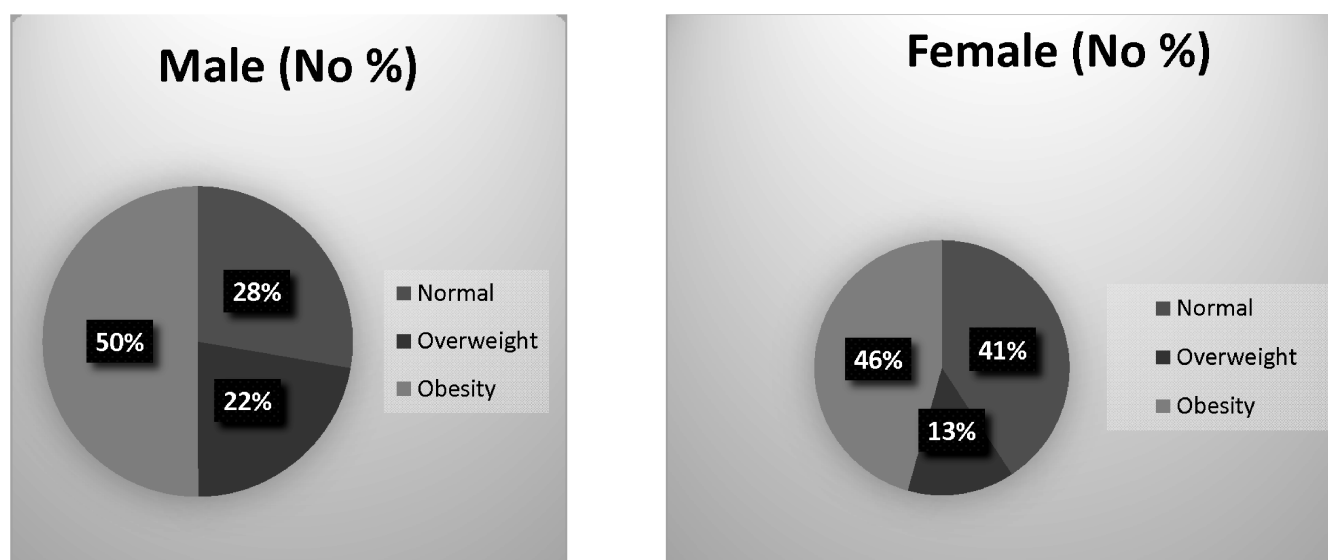


Figure 1 : The above figure shows that only 28 % of all men had normal BMI and 22 % were overweight and 50% were obese. Among all the women participants 41% of them were of normal BMI, 13 % were overweight and 44 % were obese.

Table 1: Distribution of BMI according to the age of the Respondent

BMI	Age		Total
	20-23 (%)	24-25 (%)	
Underweight	0	0	-
Normal	29(40.8%)	9(30%)	38(37.6%)
Overweight	12(16.9%)	4(13.3%)	16(15.8%)
Obesity	30(42.2%)	17(56.6%)	47(46.5%)
Total	71(100)	30(100)	101(100)

Among the dietary pattern health related information (figure 2) most of them has mentioned they do watch advertisement 95 out of 100 and among them 45.2% are obese but among 95 only 13 believes advertisements are truthful. The major sources 80% of advertisement they have discussed are the internet-based websites.

A huge percentage can be seen in consumption of ready to eat foods 77 out of 101 respondents. Among these 48% are obese and it possess a risk factor for malnourishment. Many studies have revealed as well consumption of ready to eat meals are associated with higher energy intake with poor nutrition recommendation leads to fat deposition.(Rounsefell et al., 2020b) A noticeable thing has been observed regarding the frequency among them it is quite high.

A significant observation has been seen processed food intake in 86 out of 101 respondents, among them 45.3% are obese and frequency they are having minimum 1 day /week. The trend has been increasing as per capita consumption is increasing. Even consumption of ultra-processed foods have increased by 40% from 1960 - 2010(A New Model for News Studying the Deep Structure of Young-Adult News Consumption 2008). Here maximum indulgences are bread (88.8%) followed by cookies /biscuits (79.8%)

Weight loss food consumption pattern has noticeable numbers as well as these are widely advertised on media

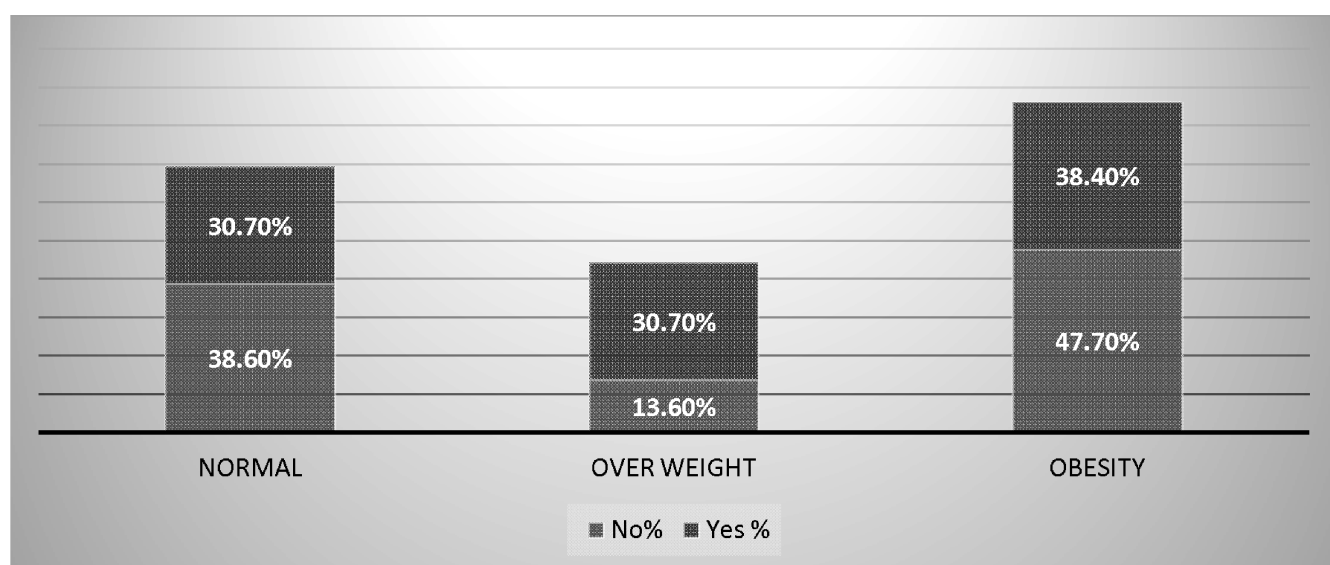


Figure 2 : Distribution of BMI according to the believe of the advertisement of the Respondent

nowadays because of the deceptive advertisements and exposure is more to females than males (Cawley et al., 2011)

A good significant mass number is also admitting that they are getting affected by the advertisements as it builds perceptions on mind of the consumers about a particular product and they make a relation between the two to buy the products (Cawley et al., 2011)

In consumption pattern most of the respondents (figure 3) gets influenced by their family members followed by sports person (41.2%). Many previous researches have claimed this happens because of lasting memory trace and of course with purchase behaviours and impacts (Pal, K., & Pal, T..)

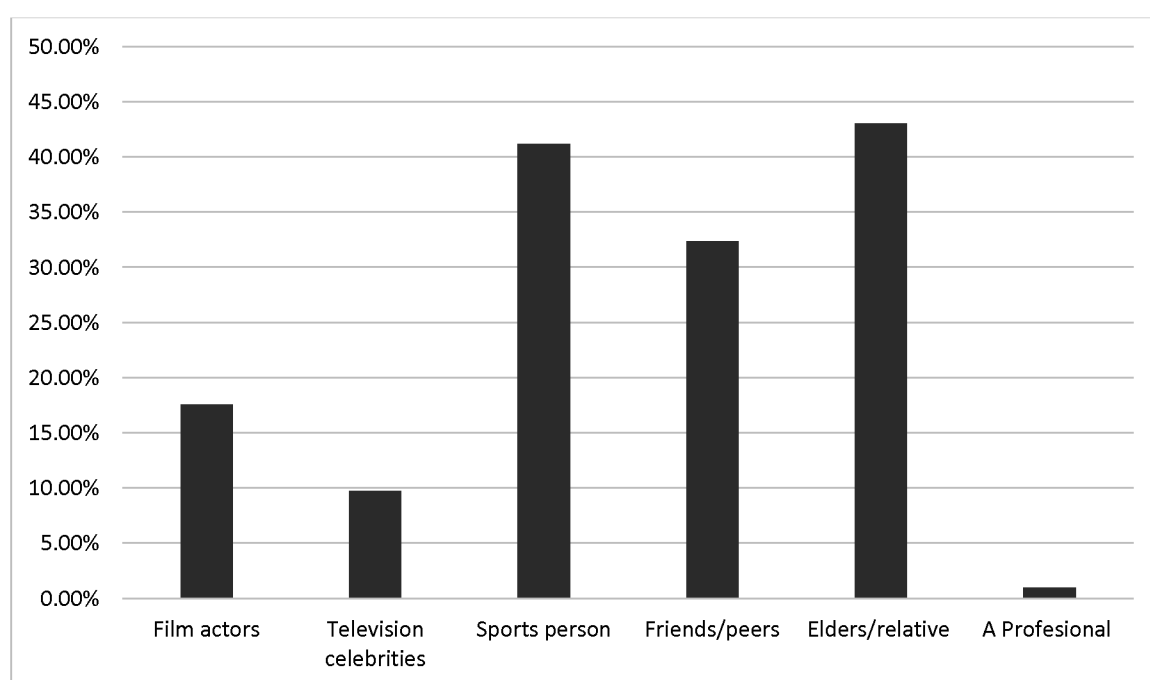


Figure 3 : Distribution of Health point of view consumption of the Respondent

Conclusion

Media content, advertisement strongly affects the dietary patterns of young people which leads to malnutrition primarily. Most of them get highly influenced by sports person followed by celebrities. This might be because they relate the sports celebrities more with fitness. But additionally they are also consuming ready to eat food or outside foods under the influence of the advertisements. From health point of view there is a huge indulgence in processed foods, ready to eat foods and even on junk foods. Hence, it is very important for the qualified professional to play an active role in the present scenario and discuss with the masses through campaigns and positive advertisements.

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The impact of pesticide residues in food crops on human health

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ABSTRACT :

Agriculture is the base of economy in many countries and India is one of them. Pesticides are widely used for pest management, increasing the crop yield and catering the huge supply of food products. Among all the pesticides used in the world, approximately 70% are used by the developed countries and the developing countries use 30%. Excessive use of pesticides leads to the accumulation of pesticide residues in the food crops. This is extremely toxic to environment as well as to humans. Ingestion of the foods having pesticide residues have been associated with several diseases like diarrhoea, dizziness, thyroid, reproductive effects and endocrine disruptions. The impact of pesticide residues can be minimised by taking certain measures like the rational use of pesticides, use of organic farming methods over conventional methods, use of bio pesticides and proper implementation and amendment of pesticide related laws. The present article has been planned to review the various aspects of pesticide residues, their accumulation in food crops, hazardous effects on environment as well as human health and the possible preventive measures to reduce the toxicity. When the developed countries are concerned about dietary pesticide consumption and its effect on the consumer's health, limited studies have so far been conducted apparently in India to understand the same. Thus, the impact of pesticide residues should be minimised by taking the preventive measures like increasing the use of bio pesticides, increasing the production and consumption of organic crops, washing and proper processing of foods and strictly implementing the pesticide related laws and increasing awareness among the consumers as well as the farmers.

KEYWORDS : Hazards, human health, organochlorines, lindane, Parkinson's disease, infertility, cancers, biopesticides, organic farming, Pesticide management bill.

INTRODUCTION

Agriculture is the base of economic growth and development. In rural areas, this is the main source of living and income. It also ensures the availability of food for rural as well as urban population [1]. The term "pesticide" covers a broad variety of compounds, which includes insecticides, fungicides, herbicides, rodenticides, molluscicides, nematicides, plant growth regulators and others [2]. Based on chemical structures, pesticides are classified as organochlorines, organophosphates, carbamic and thiocarbamic derivatives, carboxylic acids and their derivatives, urea derivatives, heterocyclic compounds, phenol and nitrophenol derivatives, hydrocarbons, ketones, aldehydes and their derivatives, fluorine containing compounds, copper containing compounds, metal organic and inorganic compounds and natural and synthetic pyrethroids [2].

Ever since the origin of civilisation, the major task of human has been to get engaged in a continuous endeavour to improve their living conditions [2]. The main tasks in which the human beings have involved themselves is securing the relief from hunger, and secondly, the control of insects, weeds, fungi and other pests of economic or public health. This is of utmost importance to our government [2]. The moment the farmers plant seeds in the ground, the crop's potential becomes vulnerable to multiple pests including weeds and insects and thus becomes threatened [4]. The developing countries have been using 108 kinds of insecticides, 30 kinds of fungicides, 39 kinds of weedicides, five kinds of acaricides and 6 different kinds of rodenticides [1]. Brazil is

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a major food producing country, which uses large amounts of pesticides in the food crops. India is in the seventh position in the use of pesticides [3]. Though pesticides are very much valuable in the developing countries, many pesticides are harmful to the environment and are known to be toxic to human beings and other non-target organisms [3].

It is observed that more than 95% of sprayed insecticides and herbicides reach a destination other than their target species, including non-target species, air, water and soil [1]. According to the World Health Organization, the most commonly consumed food groups are the fruits and vegetables and this contribute on an average, 30% of the food consumption. Since fruits and vegetables are consumed raw or semi processed, they are expected to contain higher amounts of pesticide residues as compared to other food groups of plant origin [1]. Because of their high market value and less knowledge about the toxic effects, there is no proper pre-harvest period followed after their use on vegetables and fruits [1]. The present article has been planned to review the various aspects of pesticide residues including accumulation of pesticide residues in food grains, various hazards to human health due to pesticide residues and the preventive measures for the minimisation of the impact of pesticide residues on human health.

DATA SYNTHESIS

Relevant published articles were summarized by performing computerized literature searches based on different keywords like organophosphorus compounds, organochlorines, lindane, Parkinson's disease, infertility, cancers, biopesticides, organic farming, Pesticide Management Bill. Selection of potential studies with original data were done and incorporated in the current scenario on pesticide residues and possible health hazards.

PESTICIDE RESIDUES IN FOOD CROPS

The pesticides or metabolic products of pesticides that remain in food grains, vegetables and fruits after they are applied to the crops are called the pesticide residues [2]. Due to the protective health effects from non-communicable diseases, consumption of fresh fruits and vegetables is encouraged by the governmental health agency campaigns [6]. Many of the pesticides, which are older and cheaper, such as dichlorodiphenyltrichloroethane (DDT) and lindane, can remain in soil and water for years and these chemicals have been banned by countries who signed the 2001 Stockholm Convention which is an international treaty that aims to eliminate or restrict the production and use of persistent organic pollutants [5]. In India, sulphur, endosulfan, methyl parathion, monocrotophos, cypermethrin, isoprothion, chlorpyrifos, malathion, carbendazim, butachlor, quinalphos, copper oxychloride, and dichloro are the most consumed pesticides for vegetables, fruits and food grains [2]. Food Safety and Standards Authority of India has set the maximum residue limits for pesticides in crops, foods, vegetables and fruits for production in India [2]. According to a study conducted in Pakistan, six pesticides which include Emamectin, Bifenthrin, Dichlorvos, Glyphosate, Imidacloprid, and Difenconazole were detected in different samples of fruits, vegetables, soil and water. Out of these, Emamectin was found in the water samples of orange, guava, grapefruit and carrot. Glyphosphate, a fungicide was detected in orange, grapefruit and guava samples. In vegetable samples, residues were found in carrot and turnip. The concentration of Imidacloprid, an insecticide, was detected in spinach, bitter gourd, mustard plant, beetroot and guava. The residue of Difenconazole, a fungicide, was detected in oranges, guavas, lemons and mustard plants. The highest concentration of this compound was found in vegetable crops like carrots, mustard plants and spinach. Dichlorvos was found in guava only. The residues of these pesticides in the food crops were much higher as compared to the standard limits set by MRLs [1]. According to a study in Poland which was conducted taking 380 samples of the cereal grains, the smallest portion of pesticide residue was found in mixed cereal grains (below 10%) and Avena grains (below 15%), whereas, Hordeum and Triticum grains had the highest content of pesticide residues (over 50%) [2]. A study in Kuwait revealed that out of 150 samples of fruits and vegetables taken for study, the pesticide residues were not detected in 62 samples (42%) while detected in 88 samples (58%). Out of these pesticides residue contained samples, the percentage of contamination was high for all vegetables except for carrot, zucchini and cabbage. The highly contaminated samples were tomato (88%), bell pepper (83%) and cucumber (87%) [7].

TOXIC EFFECTS OF PESTICIDES ON HUMAN HEALTH

Despite having plenty of benefits, pesticides can be extremely toxic to environment as well as human beings. Less than even 1% of the total amount of pesticides used to control weeds and pests reach the target pests [8]. Pesticide residues can have short-term adverse health effects or acute health problems like stinging eyes, rashes, blisters, nausea, dizziness and diarrhoea [9]. The chronic adverse effects can occur even after months or years of exposure and these include cancers and other tumours, damage to brain and nervous system, birth defects, infertility and other reproductive problems, damage to liver, kidneys and other organs and in severe cases, it can even lead to death [9].

The class of pesticides are associated with decrease in insulin secretion, disruption of normal cellular metabolism of carbohydrates, proteins and fats, and effects on mitochondrial functions causing cellular oxidative stress and problems to nervous and endocrine systems [10]. Carbamates are the insecticides that produce clinical signs and symptoms of cholinergic excess. The signs are somewhat similar like organophosphate toxicity, except that the effects are more reversible and less severe [8]. They have the ability to induce apoptosis and necrosis in human cells, neurobehavioral effects and increased risk of dementia and non-Hodgkin's lymphoma [10]. Organochlorines are the commonly used insecticides. They persist in the environment and tend to accumulate in the tissue as they pass up the food chain [9]. They are extremely hazardous, still less toxic than organophosphates and carbamates [8]. The exposures to organochlorines are caused through ingestion of contaminated food or water, inhalation of vapour, and absorption through skin. This pesticide has been linked with cancer, asthma, diabetes and growth disorders in children [8]. Pyrethroids are the organic compounds which are similar to the natural pyrethrins produced by the flower *Chrysanthemum cinerariaefolium*. These are the synthetic copy of a natural poison [9]. They have the ability to damage DNA in human sperms, raising concerns about possible negative effects on human reproductive health [10]. Triazines are another class of pesticides which are effective, inexpensive and are generally used as herbicides. Human exposures to triazines have been associated with endocrine disruption, reproductive toxicity and carcinogenicity [8, 10].

NEURONAL DAMAGE DUE TO PESTICIDES

Epidemiological studies suggest that pesticide exposure to humans can be significant risk factor for neurological disorders, including Parkinson's disease, Alzheimer's disease and multiple sclerosis [11]. Due to the similarities in brain biochemistry, such pesticides become neurotoxic to humans [11]. Studies suggest that exposures of pesticides through occupational hazards tend to be significantly higher than that ingested by general people through food. The enzyme acetylcholinesterase is the primary target of organophosphate. Inhibition of acetylcholinesterase causes accumulation of acetylcholine at cholinergic synapses, which leads to over-stimulation of muscarinic and nicotinic receptors [12]. Many studies have demonstrated that beside organophosphates, organochlorine and pyrethroids which are frequently used in agriculture are linked with adverse neurological problems. [12].

REPRODUCTIVE DISORDERS

Many study results have shown that increase of insecticides in blood levels in vertebrates cause reproductive dysfunction. For human beings, it is suggested that consumption of foods like fish, chick and goat containing beyond permissible limit must be avoided [2]. Triazines, such as atrazine, simazine and ametryn are a class of pesticides which are related to reproductive toxicity and cause delay in sexual maturity [10]. Pesticide exposures cause sterility in humans. Many males become unable to have children because they lose the capacity to make sperms [13]. Synthetic pyrethroids, such as fenvalerate, permethrin, sumithrin are known to cause DNA damage in human sperms, raising concerns about possible negative effects on human reproductive health [10]. If these harmful chemicals enter a woman's body, this may appear in her breast milk later. The women, who get exposed to these pesticide residues before pregnancy, may have a miscarriage or the baby may be born dead because these toxic chemicals affect the hormones which are responsible for growth and reproduction [13].

OXIDATIVE STRESS

Reactive Oxygen Species (ROS) are the free radicals, that is, the oxygen containing species having an unpaired electron, such as superoxide (O_2^-). These are highly unstable in a chemical sense. Exposure to pesticides cause over production of these reactive oxygen species in the tissues which cause extensive DNA damage and protein damage in cells [14]. Oxidative stress has been reported as the main mechanism of organophosphate toxicity [2]. Oxidative stress is defined as the imbalance between the production of free radicals capable of causing lipid peroxidation and the body's antioxidant defence mechanism [15].

DEVELOPMENT OF CANCERS

Increased exposure to the agrochemicals is the most important risk factors for cancers among agricultural workers [16]. Studies have shown that the risks of developing various types of cancers are highly associated with the consumption of specific products, which have some pesticide residues such as dichlorodiphenyltrichloroethane, and these products include fish, water, seafood, milk and other dairy products [2]. A study report says that people aged 65 and above are having more chances of developing these types of cancers than other adult groups, because they consume more fruits and vegetables, thus maximising the exposure to pesticide residues [17]. A study conducted in Iran reveals that some of their widely used pesticides like amitraz, dichlorvos, diazinon, permethrin, chlorothalonin, meta-sodium were classified as possible human carcinogens by the United States (US) Environment Protection Act (EPA) [16].

MEASURES TO REDUCE PESTICIDE RESIDUES IN FOOD CROPS

India is the second most populous country in the world and nearly 64% of its population is dependent on agriculture [18]. So food security is one of the major concerns for India and for the whole world as well [18]. For the prevention of crops from pests, insects and weeds, different types of pesticides are used for different types of crops [2]. Nearly 70% of the total pesticides used in the world are applied in developed countries and the rest 30% are applied in the developing countries [18]. In order to reduce the risks, sensitization of farmers to better pesticides, safety practices and the need for continuous monitoring of pesticide residue is highly recommended [7]. It is very well known that pest management is one of the major inputs of agricultural production, therefore, this area needs great attention to economise the production, as well as, to provide safe foods and lower the medical expenses for treating the resulting ailments [18]. Various strategies are there which can be used to minimise the pest and disease problems and reduce pesticide residues in food grains, vegetables and fruits [2].

ORGANIC FARMING

The use of organic foods in place of non-organic ones is one of the widely used methods now a day to reduce the effect of pesticide residues in food crops [2]. The use of synthetic pesticides is restricted in organic agriculture. While in conventional agriculture, the pesticide residues in fruits and vegetables constitute the main source of human pesticide exposure [19]. According to standard Meta analyses, the frequency of occurrence of detectable pesticide residues was four times lesser in non-organic crops than organic crops [2]. Many studies have shown that there is a positive correlation between the use of organic foods and good health [19]. On an average, organic crops have higher concentration of antioxidants than non-organic crops. It is always advisable to consume more foods, which are rich in antioxidants. Antioxidants reduce the effects of chronic diseases by suppressing the oxidative activities. Increasing the dietary intake of antioxidant rich foods can fight against cardiovascular diseases, certain cancers like prostate cancers and neurodegenerative diseases [2]. India stands at a unique position in organic agriculture. It has 6,50,000 organic producers, 699 processors, 699 exporters and 7,20,000 hectares of land under cultivation. India produced certified organic products, which include all varieties of edible products like sugarcane, oil seeds, cereals and millets, cotton, pulses, medicinal plants, medicinal plants, tea, fruits, spices, vegetables, coffee etc [20].

THERMAL TREATMENT

Thermal treatment of food is done in many ways including drying, pasteurization and sterilization, blanching, steaming, frying, boiling, cooking, depending upon the nature and processing of food [21]. Drying is a simple and traditional method and this process has been found to reduce pesticide residues considerably. Pasteurization and sterilization are the commercial thermal processing techniques which are capable of reducing the amount of diazinon, malathion, chlorpyrifos and lindane. Frying can significantly reduce the residues of thiabendazole, technazene, chlorpropham, and maleic hydrazide. Reports show that blanching, steaming, and boiling, cooking, frying, roasting and baking play significant roles in reducing the pesticide residues from foods. Boiling may remove 35 to 60 percent of organophosphate residues and 20 to 25 percent of organochlorine residues. Thermal processing affects the pesticide residues in foods of animal origin as well. Cooking by scrambling can reduce approximately 38% of chlorpyrifos from eggs, while hard boiling can eliminate all pesticides in shell [2, 18,21].

BIOPESTICIDES

Biopesticides are a group of pest management agents which are used in Integrated Pest Management (IPM). Biopesticides are defined as a mass produced agent manufactured from a living microorganism or a natural product for the treatment of pests. Biopesticides are classified into three different types according to the active substance – micro-organisms, biochemicals and semiochemicals. Microorganisms like bacteria, fungi, oomycetes, viruses and protozoa are used for the biological control of pests, insects and weeds. The mostly used microbial biopesticide is the insect pathogenic bacterium *Bacillus thuringiensis* (Bt). Plants produce a wide variety of secondary metabolites which can be used as biopesticides. They have low mammalian toxicity. A semiochemical is a chemical signal produced by one organism to cause a behavioral change in the individual of the same or different species. The most widely used semiochemical for crop protection are the insect pheromons. Biopesticides are selective; produce little or no toxic effects, developmental costs are also significantly lower than those conventional chemical pesticides, and these properties make them good components of IPM [22].

IMPLEMENTATION AND AMENDMENT OF PESTICIDE RELATED LAWS

Pesticide registration is a scientifically based, legal and a complex process which takes considerable time, resources and expertise on the part of the registration authority, manufacturing industries and various public interest groups. Here, a wide variety of effects associated with the use of pesticide product and its potential effects on human health and the environment is assessed [23]. In India, pesticides are regulated through the Insecticides Act, 1968 and Insecticides rule, 1971. The parliamentary approval of the Pesticide Management Bill is still waiting since 2008. The Draft Pesticide Management Bill was released by the Union Ministry of Agriculture and Farmers Welfare (MoFAW) on 19th February, 2018. Subsequently, a new Pesticide Management Bill has been created and now approved by the Union Cabinet on 12th February 2020 [24]. The pesticide related laws must be strictly implemented and amended in order to reduce the cases of pesticide residues in food crops [2].

PRESENT SITUATION IN INDIA

The long-term safety of pesticide consumption through conventional food production has been questioned, with evidence from long-term cohort studies covering areas ranging from possible neurotoxicity to endocrine disruption [25]. A number of widely used pesticides have been banned retrospectively when unexpected negative health impacts have been identified [26, 27]. From a regulatory perspective, dietary intake of pesticides is not considered to pose a health risk to consumers as long as individual pesticide concentrations in foods are below the Maximum Residue Level (MRL). Surveys conducted by the European Food Safety Authority and the US Department of Agriculture show that the vast majority of foods contained individual pesticide levels below the MRL, but at 1.7% (European) and 0.59% (US), respectively, found to exceed the limits. It was also found that 30.1% and 27.5% of food samples analyzed contained multiple pesticide residues [28, 29]. There is considerable controversy about health risks posed by chronic low-level dietary pesticide exposure [30–32], whilst lower

levels of pesticide residue excretion are consistently observed during organic diet intakes [33-35]. It is not clear how this impact the health of the consumers. Interestingly, a recent study by the FSSAI revealed that out of 23,660 samples from 12 States of India 19.1% have pesticide residue, while 2.2% are found to have higher than MRL (FSSAI Report, 2019 File No: 07(5)2019/pesticide residues/RCD/FSSAI). Thus, this indicates that the study is grossly insufficient in the context of nearly 140 crores of population over the country. Hence, FSSAI should consider extending the present study all over the country covering at least 20% of the population to obtain reasonably scientific data to understand the gravity of the problem. It is particularly essential with respect to the growing incidence of life-style disorders like atherosclerosis, CVD, COPD, Cancer, Diabetes, neurological diseases etc. When the developed countries are concerned about dietary pesticide consumption and its effect on the consumer's health, limited studies have so far been conducted apparently in India to understand the same.

CONCLUSION

Though the use of pesticides is effective in the field of agriculture for increased productivity, using it more than the recommended level leads to the accumulation of pesticide residues in food grains including fruits and vegetables. When humans ingest these food grains, they become toxic for the human health causing several acute and chronic problems. Thus, the impact of pesticide residues should be minimised by taking the preventive measures like increasing the use of biopesticides, increasing the production and consumption of organic crops, washing and proper processing of foods and strictly implementing the pesticide related laws and increasing awareness among the consumers as well as the farmers. Pesticide users should be concerned about the risks and how to handle it properly. They must use personal protective equipment, which is implemented scientifically in reducing health hazards.

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Anti-aging Treatments: An Essential Part of Modern Lifestyle

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Abstract :

Skin, the largest organ of the body, is the most obvious place to observe signs of ageing. With advancing age, skin shows the sign of ageing like wrinkle, loss of elasticity, rough texture and laxity etc. Both extrinsic (UV radiation, smoking,) and intrinsic factors (Structural change in extracellular matrix component) affect aging; aging due to extrinsic factors are more prominent than the intrinsic ones. Mainly UV radiation increase the level of reactive oxygen species which changes the composition of essential extracellular matrix components such as collagen and elastin. This review mainly discusses these factors and the strategies used in antiaging products to overcome/ minimize the effect of ageing.

Keyword: Aging; anti-ageing; collagen; elastin; antioxidant, UV protection; moisturizer; botulinum toxin; laser; Cosmetics;

Introduction

Desire to look beautiful and young is an universal aspiration of the humankind. Aging of the organs begins from the day, when one is born, skin is no exception to that. In fact, effect of environment explicitly is felt on the skin. Most of the vital organs are protected within the body but unfortunately skin is exposed. It directly interacts with the environment and absorbs the harmful rays of sun, chemicals which pollute the air, smoke etc. This results in pigmentation, wrinkles and dryness, robbing the skin its natural freshness- which is very similar to natural aging which happens due to change in composition. These changes has become an unofficial indicator of age and humans since time immemorial have been trying to camouflage changes through a variety of strategies. The most primitive of these strategies is anti-aging cosmetics.

Use of cosmetics can be traced back to the beginning of human civilization. Cleopatra, the queen of Egypt, is probably the first person we think of, when ancient beauty regimes are explored. She used to take two bath with donkey milk a day, which is a rich source of alpha-hydroxy acids, vitamins; molecules having skin rejuvenating properties. Tang-dynasty ruler and sole female emperor of China, Wu Zetian has developed an anti-aging formula called as fairy powder. But cosmetics, once the privilege of the royal people is now extended to commoners. Cutting across the social and economic divide, the demand for anti-aging products is increasing in all sectors of the society. Development of anti-aging formulations has become a prime research activity and newer formulations are hitting the market every now and then. The objective of this article is to understand the science behind these anti-aging products.

Reasons behind skin aging—

Skin aging is a complex biological process, influenced by a combination of endogenous (genetics, cellular metabolism, hormone) and exogenous (chronic light exposure, pollution, ionizing radiation, chemicals, toxins, smoking) factors [1]. Collagen, a protein present in the extracellular matrix, plays an important role in maintenance of skin structure. Predominantly present in the dermis, the collagen content of the skin decreases by 1% per year throughout adult life [2]. Another molecule, elastin is also supremely important for elasticity of the skin. Elastin

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enables the skin to regain its shape after deformation. However, turnover of elastin is very slow, overall half-life being similar to human life span. Collagen is responsible for retention of water. As a person ages, the nature of collagen changes; from well-organised bundles of fibres it changes to become fragmented and dis-organised fibres; also loses its interwoven extensions with elastin fibres. As collagen fibres decrease in number, their capacity to bind water decrease and the skin loses elasticity and becomes wrinkled. With advancing age, there is a loss of dermal volume, and dermal thickness decreases by about 20% and 50%. Intrinsic ageing occurs due to reduction in the contact between the epidermis and dermis. Rete ridges (epithelial extensions that project into the underlying dermis) are reduced, resulting in reduction and supply of oxygen and nutrient to the epidermis [3-4].

Extrinsic skin ageing is caused by environmental factors. Over 80% of facial skin ageing is due to low-grade chronic UV exposure which induces production of reactive oxygen species. This affects the epidermis, causing irreparable damage to cellular DNA. Exposure to UV radiation increases skin pigmentation due to increased proliferation of melanocytes [5-7].

Extrinsically aged skin is characterised by mainly coarse and deep wrinkling, rough texture, telangiectasia (spider veins), irregular or mottled pigmentation, a sallow or yellow complexion and a loss of elasticity. The severity of extrinsic ageing mainly depends on skin types; fairer skin is affected more than darker skin [8].

Method to overcome aging—

Strategies to overcome aging include both prevention and cure. The simplest as well as most used strategy is the change in life style.

Change in lifestyle

Prevention is always better than cure. Changing lifestyle to prevent premature skin aging is a time-tested strategy. Sunlight is the source of UV radiation, daily use of a proper sunscreen with at least SPF 15 (sun protection factor) is helpful to protect the skin. A sunscreen with moisturizer is the best choice as moisturizer traps water and gives skin a more youthful appearance.

Avoidance of smoking is also recommended. Chronic exposure to chemicals contained in cigarettes that can cause wrinkles and make the skin dull. The same is also valid for drinking alcohol as it dehydrates the skin, and make it lifeless.

Fruits and vegetables are always best for health and skin is no exception; it may prevent premature skin aging as they contain vitamin and minerals. American Academy of Dermatology says a diet containing lots of sugar or other refined carbohydrates can accelerate aging.

Exercise can improve circulation and boost the immune system which in turn may give the skin a more-youthful appearance. Some facial exercises are also helps to recover saggy skin.

Washing the face gently with water (not to damage the skin) can reduce the chances of wrinkle. Gentle washing helps to remove pollution, makeup, and other substances without irritating skin.

Cosmetics (Topical application)

Anti-wrinkle creams, protect from sun damage, moisturize the skin and also brighten it up. They have a combination of anti-aging, moisturizer, skin brightener and sunscreen molecules.

Anti-aging molecules

According to the function and effect, anti-aging constituents can be divided in group like antioxidant, moisturizer, collagen producer, sunscreen, depigmenting agent.

Antioxidants are the main component of anti-aging formulation. They inhibit or delay oxidation of a substrate

while present in minute amount. ROS can make skin bleak looking and water lacking. Therefore, it's necessary to pay attention to the nutritional antioxidant when body's endogenous antioxidant failed to control ROS. Vitamin E, vitamin C, idebenone, coenzyme Q10, ferulic acid, , zinc sulfate, green tea, superoxide dismutase, carotenoids and polyphenols are used for scavenging free radicals. They directly neutralize free radicals or they reduce the membrane peroxides or they quench iron to decrease ROS production. Vitamin E continue to accumulate by penetrating the skin and therefore skin becomes soft and smooth. For light aging vitamin E is a good agent. Sunscreen work better when vitamin E is combined with vitamin C. In addition, vitamin E also acts as anti-aging, inhibiting erythema solare, reducing wrinkles and its anti-inflammatory effects [9-10]

Decrease in dermal collagen leads to decline in skin elasticity and therefore wrinkles appear. So, promoting of the growth of collagen can also alleviate the aging of the skin. Vitamin A, retinoic acid, cell growth factor, tartaric acid, alpha and beta hydroxy acid, beta glucan etc. promote the growth of collagen. Research indicates that the Vitamin A have the ability to promote the synthesis of collagen and reduce hyper pigmentation and also inhibit enzymes from breaking down collagen Vitamin A can enhance the skin elasticity, improve complexion and skin texture Retinoic acid is likely to contribute retention of water to increase skin softness [11]. Alpha hydroxy acids (such as glycolic acid, lactic acid, citric acid, malic acid and so on) and Beta hydroxyl (Salicylic acid, beta hydroxybutanoic acid, tropic acid, trethocanic acid) stimulate the exfoliation of epidermal cells in the stratum corneum. This results in the sloughing off dull and rough skin and promotes cellular renewal. Long-term use of these agents can improve the skin wrinkles, roughness and colour due to light, and may also increase the thickness of epidermis, dermis, and collagen synthesis induced by the increased water retention, thereby improving the elasticity of the skin and appearance [12-13].

The UV radiation is one of the greatest causes of skin aging as it damages DNA directly causing apoptosis or growth arrest. To protect skin from this light damage a proper sunscreen with perfect SPF as per age is necessary. Using ultraviolet light scattering agent can reduce skin damage caused by the sun. At least SPF 15 should be used to get protection from sun damage [14]. The compound in sunscreen includes titanium dioxide, zinc oxide, oxybenzone, octocrylene etc.

With advancing age, water retention power of skin decreases and this leads to the decline of protease activity, causing skin peeling. So moisture is an essential part of anti-aging products. The ingredients used for moisturizing attracts water to the horny layer to increase the skin moisture content. The agents used for this purpose are sorbitol, glycerol, polyethylene glycol, cholesterol and oleic acid, hyaluronic acid, lactic acid, pyrrolidone carboxylic acid salt, and some microbial fermentation metabolites. Hyaluronic acid a natural skin component is the most used, of them all, which is produced synthetically [15].

Skin lightening or skin brightening agent are also used to get a natural looking skin and to minimize age spot. They minimize the melanin production in the skin which results by sun exposure. The ingredients include hydroquinone, kojic acid, licorice extracts, aloe gel etc.

Cure

Invasive procedures

In invasive procedure they resurface the epidermis to remove the damaged epidermis and replace the tissue with remodelled skin layers and sometimes help in formation of new collagen. With the growing technology and science, lot of possibilities exist in this field.

Chemical Peels

By the use of chemical solution, the outer layer of the old skin is removed and new skin is replacing the damaged one. The new skin is usually smooth and less wrinkled. Chemical peels are classified into three categories. Superficial peels [á-â-, lipo-hydroxy acids, trichloroacetic acid 10–30%] exfoliate epidermal layers without going beyond the basal layer. Medium-depth peels (trichloroacetic acid above 30 to 50%) reach the upper reticular dermis, deep peels (trichloroacetic acid > 50%, phenol) penetrate up to the lower reticular dermis.

Superficial peelings target the corneosomes, causes increase epidermal activity of enzymes, it leads to epidermolysis and exfoliation. Medium-depth peels cause coagulation of membrane proteins, destroy living cells of the epidermis and, depending on the concentration, the dermis. Deep peels coagulate proteins and produce complete epidermolysis, restructure of the basal layer and restoration of the dermal architecture. Chemical peels can be used to treat: Fine lines around the mouth and under the eyes, wrinkles, mild scarring, age spots, sun damage, and the overall look and feel of the skin [16,17].

Visible Light (IPL, Laser)

Nonablative skin rejuvenation is a low risk and short downtime technology which can improve aging structural changes without disruption of cutaneous integrity. Synthesis of new collagen is induced by heat denaturalization of dermal collagen. This is a controlled form of skin wounding aimed at achieving a more youthful appearance after the wound heals [18]. The epidermis and superficial dermis can be selectively damaged by two basic mechanisms: by targeting discrete chromophores in the dermis or at the dermal-epidermal junction and by utilizing mid infrared (IR) lasers. Treatment of photo aged skin has been divided into Type I – Treatment of ectatic (distended) vessels and erythema, irregular pigmentation, and pilosebaceous changes and Type II - improvement of the dermal and subcutaneous senescence [19-20].

Lasers emitting light at 532-, 585-, 595-, 755-, 800-, and 1064-nm wavelengths as well as filtered light generated by IPL systems (Intense pulse light) are used to treat vascular and/or pigment irregularities. In Type II photo rejuvenation, Lasers emitting 1320, 1450 and 1540 nm target interstitial and intracellular water as chromophores and pulsed dye lasers (PDL) that target oxyhemoglobin as the primary chromophore are employed. IPL devices (non-laser high intensity light sources) is less effective comparing to laser technology for reducing wrinkle [21].

Skin exposed to the thermal stress shows a wound healing response ultimately leading to re-epithelization and dermal remodeling [22]. The recovery time could take up to a few weeks but the results are long lasting (up to 5 years). Normally, several sessions are required to achieve desired results.

Botulinum Toxin (BTX)

Botulinum toxin produced by *Clostridium botulinum* is a neurotoxin; there are seven different serotypes of BTX: A, B, C1, D, E, F, and G. They inhibit the release of acetylcholine from the presynaptic motor neuron, resulting in chemodenervation and paralysis of the treated muscle. Injected into the skin, they **block certain chemical signals from nerves, that cause muscles to contract. This causes muscle relaxation which smooths the overlying skin and reduces wrinkles** Over time, new nerve terminals form and create new neuromuscular junctions with the muscle fibers, which gradually restore motor function [23].

Results can last 2–5 months. Allergic reactions to botulinum toxin are very rare [24-26].

Filler

Products injected within the wrinkled skin can fill up the void and improve its physical features. Dermal fillers are used to plump up wrinkles, smoothen lines and restore volume in facial skin. Fillers can be made using single active ingredient or cocktails of different compounds.

Substances normally used are collagen (bovine-derived, human-derived from tissue culture), HA (HA from bacterial fermentation), autologous (fat, cultured human fibroblasts), synthetic or pseudo-synthetic implants (silicone, polymethacrylate microspheres, Poly-L-lactic acid, alkyl-imide gel polymer). Improving the biosynthetic capacity of fibroblasts, the enhancement of cell activity, increased hydration, are the main mechanisms of skin rejuvenation by this method [27,28].

This treatment usually takes less than half an hour and recovery time is minimal. Results are seen right away and last months to years depending on the type of filler and the location [29]. Fillers may be grouped into temporary, semipermanent (lasting between 1–2 y), or permanent materials (lasting longer than 2 y).

Hormone Replacement Therapy (HRT)

With age there is a progressive decrease in level of hormone. Levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1), TSH, thyroid hormones (T3), melatonin (nocturnal), , dehydroepiandrosterone (DHEA) estrogens and testosterone are decrease progressively. In human the main hormonal deficits are menopause, andropause and partial androgen deficiency of the aging male. Substitution of dehydroepiandrosterone (DHEA), a hormone produced by adrenal glands has been proven to lead to an improvement of body condition, sexual activity, bone density, and well-being [30,31].

Autologous Platelet-Rich Plasma (PRP)

Autologous Platelet-rich Plasma (PRP) has proven to have effect on skin rejuvenation. PRP is derived from fresh whole blood, which contains a high concentration of platelets. Various growth factor (GF) including platelet-derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF), are secreted from the concentrated platelets activated by aggregation inducers. PRP may induce the synthesis of collagen and other matrix components by stimulating the activation of fibroblasts, thus, rejuvenating the skin. However, the molecular mechanisms underlying PRP-inducing wound healing processes are still largely unknown and experimental studies confirming the effects of PRP on aged fibroblasts are very limited [32,33].

Conclusion

Ageing is a normal physiological processes which can't be altered but extrinsic factors can be controlled through change in lifestyle and cosmetics. Several moderately invasive procedures are also in use which can reverse the skin –aging to a certain extent. Technologies involving tissue engineering shows the promise of a more permanent solution.

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Prevalence of polycystic ovary syndrome in females in the age group of 18-30 years

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Abstract :

Menstruation is the periodic, well-ordered sloughing of the uterine lining, in response to the interactions of hormones produced by the hypothalamus, pituitary, and ovaries. The median duration of a menstrual cycle is 28 days with most cycle lengths between 25 to 30 days. Patients who experience menstrual cycles that occur at intervals less than 21 days are termed polymenorrheic, while patients who experience prolonged menstrual cycles greater than 35 days, are termed oligomenorrheic. The typical volume of blood lost during menstruation is approximately 30 ml. Polycystic Ovarian Syndrome (PCOS) is one of the most common hormonal disorders among women in the reproductive age. PCOS is commonly diagnosed in women presenting with infertility. According to American College of Obstetricians and Gynaecologists, common signs of polycystic ovary syndrome (PCOS) are irregular menstrual period, infertility, obesity, excess hair growth on the face, chest, abdomen, or upper thighs, Severe acne or acne that occurs after adolescence and does not respond to usual treatments, oily skin, patches of thickening, velvety, etc. The present study aimed to find out the prevalence of the different symptoms of Polycystic Ovary Syndrome among females in the age group of 18-30 years. The study was an observational descriptive study based on pre-tested questionnaire. Data collected through online questionnaire were put in Microsoft Excel Worksheet (Microsoft, Redwoods, W. A., USA.) and they were checked for elimination errors. Prevalence of different symptoms of PCOS were determined and judged through Bar Graphs along with frequency tables. All the statistical analysis was performed by SPSS software (Statistical Package for Social Sciences version 20.0). The study revealed that 14.9% females have irregular menstrual cycle among the participants, 28.4% females have experienced sudden weight gain, 48.6% females have experienced trouble to lose weight, 40.5% females have acne problems whereas 27% experience acne problems sometimes, 28.4% females have experience excessive body hair growth, 27% females always have unexplainable mood swings & 62.2% sometimes have unexplainable mood swings, 55.4% females always have excessive hair loss or hair thinning, 48.6% females feel fatigued mostly and 14.9% have an altered menstrual cycle of 33 days or more. The prevalence of the symptoms of PCOS has been evidently found in the study population in varying proportions.

Keywords - PCOS, Menstrual Cycle, Symptoms; PCOS.

Introduction

Menstruation is the periodic, well-ordered sloughing of the uterine lining, in response to the interactions of hormones produced by the hypothalamus, pituitary, and ovaries [5]. The menstrual cycle may be divided into two phases: follicular or proliferative phase and the luteal or secretory phase. The length of a menstrual cycle is the number of days between the first day of menstrual bleeding of one cycle to the onset of menses of the next cycle. The median duration of a menstrual cycle is 28 days with most cycle lengths between 25 to 30 days [8]. Patients who experience menstrual cycles that occur at intervals less than 21 days are termed polymenorrheic,

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while patients who experience prolonged menstrual cycles greater than 35 days, are termed oligomenorrheic. The typical volume of blood lost during menstruation is approximately 30 mL [2]. Any amount greater than 80 mL is considered abnormal [2]

Polycystic Ovarian Syndrome (PCOS) is one of the most common hormonal disorders among women in the reproductive age. PCOS is commonly diagnosed in women presenting with infertility [4]. The exact prevalence of PCOS is still not known as the syndrome is not precisely defined [4]. There are a few studies conducted in India. In a cross-sectional study conducted in Mumbai among adolescent and young girls reported prevalence of PCOS 22.5% by Rotterdam and 10.7% by Androgen Excess Society criteria. [3]

Polycystic ovary syndrome (PCOS) was first reported in modern medical literature by Stein and Leventhal who, in 1935, described seven women suffering from amenorrhea, hirsutism, and enlarged ovaries with multiple cysts [6].

According to American College of Obstetricians and Gynaecologist Common signs of polycystic ovary syndrome (PCOS) include the following :

- Irregular menstrual periods—Menstrual disorders can include absent periods, periods that occur infrequently or too frequently, heavy periods, or unpredictable periods [1].
- Infertility—PCOS is one of the most common causes of female infertility [1].
- Obesity—As many as 4 in 5 women with PCOS are obese [1].
- Excess hair growth on the face, chest, abdomen, or upper thighs—This condition, called hirsutism, affects more than 7 in 10 women with PCOS [1].
- Severe acne or acne that occurs after adolescence and does not respond to usual treatments [1].
- Oily skin [1].
- Patches of thickened, velvety, darkened skin called acanthosis nigricans [1].
- Multiple small fluid-filled sacs in the ovaries [1].

The symptoms of PCOS may vary from woman to woman [4]. The cause of PCOS is unknown but most experts suggest that there may be several factors including genetics. A main underlying problem with PCOS is hormonal imbalance. In women with PCOS, the ovaries secrete more androgens than normal. High levels of the androgens affect development and release of eggs from ovary each month (ovulation) [4]. High levels of androgens lead to the different symptoms like acne, excessive body hair, mood swings, etc.

The daily light-dark cycle governs rhythmic changes in the behavior or physiology or both of most species. Different studies have found that these changes are governed by a biological clock, which in mammals is located in two brain areas called the suprachiasmatic nuclei [9]. There was significant relationship found between disruption of different hormones like corticotropin-releasing hormone, adrenocorticotrophic hormone, prolactin, etc. in a study conducted in China which involved night shift workers and also PCOS- model rats [10]

Nutrition and PCOS are clearly interlinked and many studies have shown the same. Diet plays one of the most important roles in the treatment of PCOS. The introduction of a properly balanced diet should be the key in the treatment of women with PCOS diagnosed according to Rotterdam criteria [7].

Aim of the Study

The present study aimed to find out the prevalence of the different symptoms of Polycystic Ovary Syndrome among females in the age group of 18-30 years.

Materials and Methods

The study was an observational descriptive study based on pre-tested questionnaire. The study was conducted with all female subjects in a specific age group of 18-30 years. The duration was December 2021 to January 2022. The sample size was 74 respondents.

The study was conducted through an online survey where online questionnaire was prepared using Google Forms, using KAP (knowledge, attitude, practice) method. The method of sampling was purposive by use of social media platforms.

After receiving the filled-up forms, data-based information was statistically analyzed using SPSS software (Statistical Package for the Social Sciences) developed by IBM for data management, advanced analytics, multivariate analysis, business intelligence and generating many more types of data outputs.

Results

Data collected through online questionnaire were put in Microsoft Excel Worksheet (Microsoft, Redwoods, W. A., USA.) and they were checked for elimination errors. Prevalence of different symptoms of PCOS were determined and judged through Bar Graphs along with frequency tables. All the statistical analysis was performed by SPSS software (Statistical Package for Social Sciences version 20.0).

The age group was divided into two groups 18-24 years and 24.1- 30 years. Among the respondents 69 respondents were unmarried and 5 were married. Also, the respondents contained of 47 students, 25 working professionals and 2 others.

1. Distribution of Irregular menstrual cycle in the Study Population (N=74)

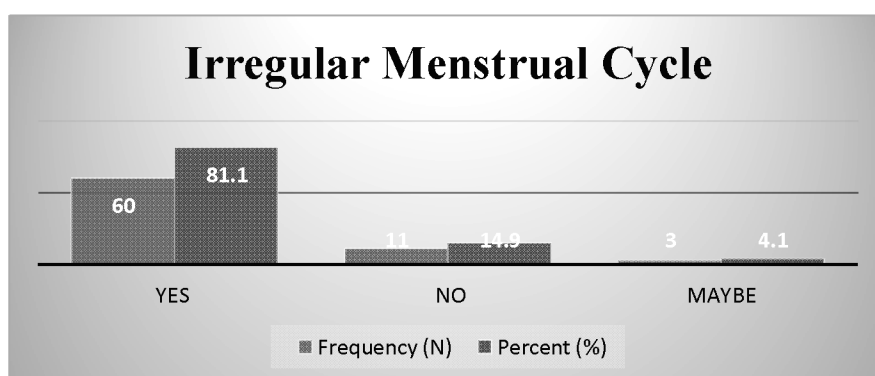


Figure 1 shows the prevalence of irregular menstrual cycle. The table shows that amongst the study population 14.9% females have irregular menstrual cycle, 4.1% are not sure whereas 81.1% have regular menstrual cycles.

2. Distribution of Sudden Weight Gain in the Study Population (N=74)

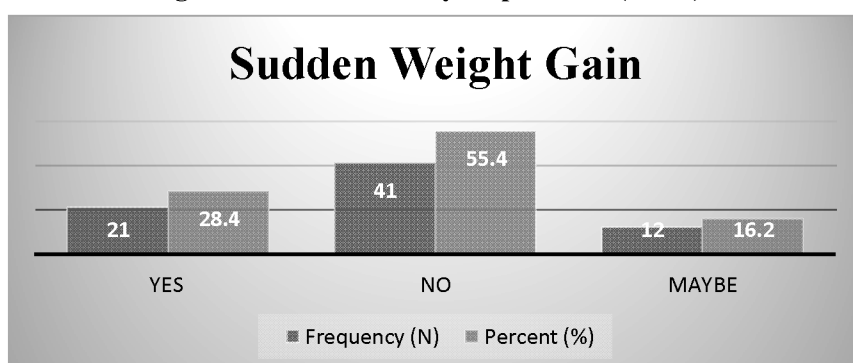


Figure 2 shows the prevalence of sudden weight gain. The table shows that amongst the study population 28.4% females have experienced sudden weight gain, 55.1% have not experienced sudden weight gain whereas 16.2% are not sure.

3. Distribution of Trouble to lose weight in the Study Population (N=74)

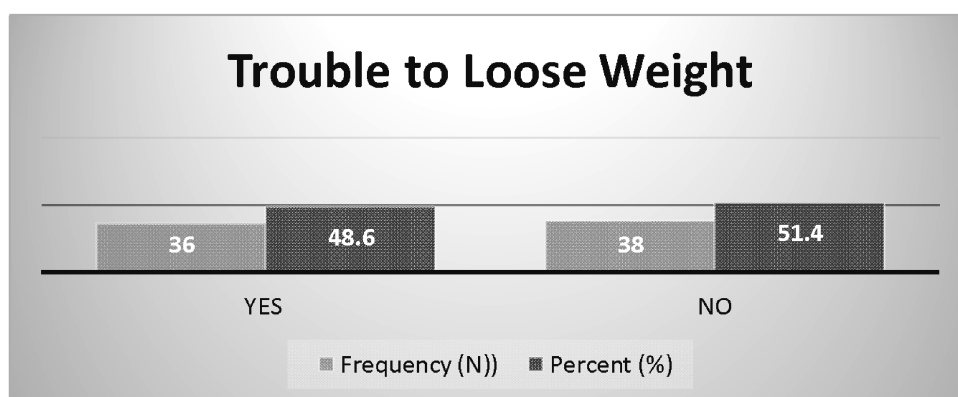


Figure 3 shows the prevalence of trouble to lose weight. The table shows that amongst the study population 48.6% females have experienced trouble to lose weight, 51.4% have not experienced trouble to lose weight.

4. Distribution of Face Acne Problems in the Study Population (N=74)

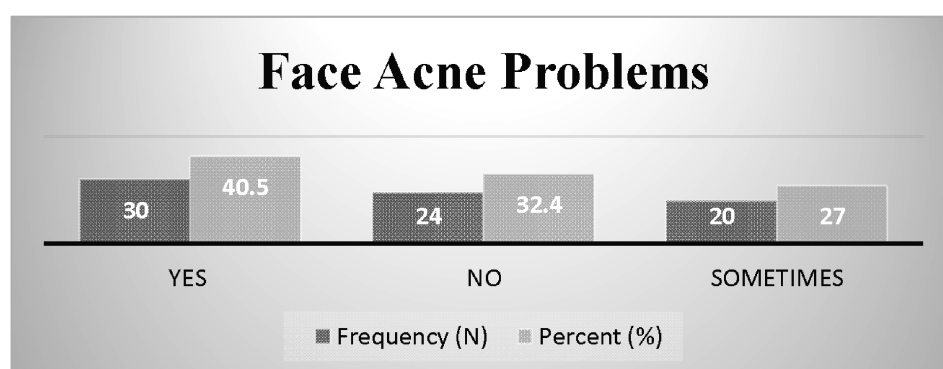


Figure 4 shows the prevalence Acne problems. The table shows that amongst the study population 40.5% females have acne problems, 32.4% do not have acne problems whereas 27% experience it sometimes.

5. Distribution of Excessive Body Hair Growth in the Study Population (N=74)

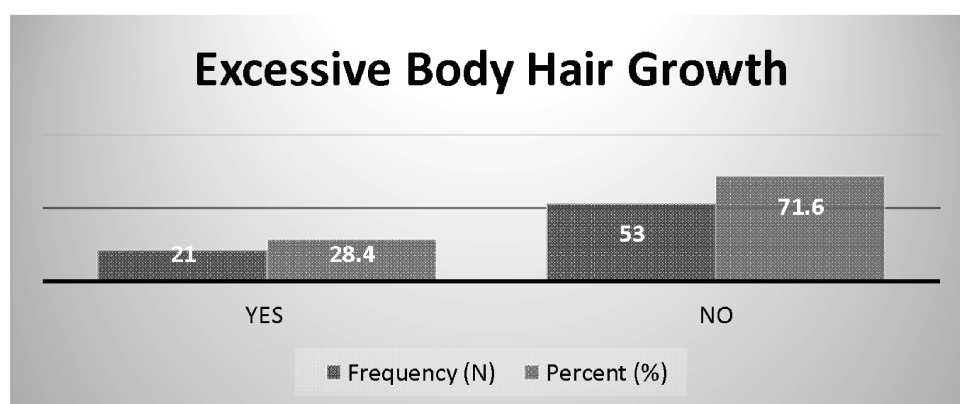


Figure 5 shows the prevalence of excessive body hair growth. The table shows that amongst the study population 28.4% females have experience excessive body hair growth whereas 71.6% do not have excessive body hair growth.

6. Distribution of Unexplainable Mood Swings in the Study Population (N=74)

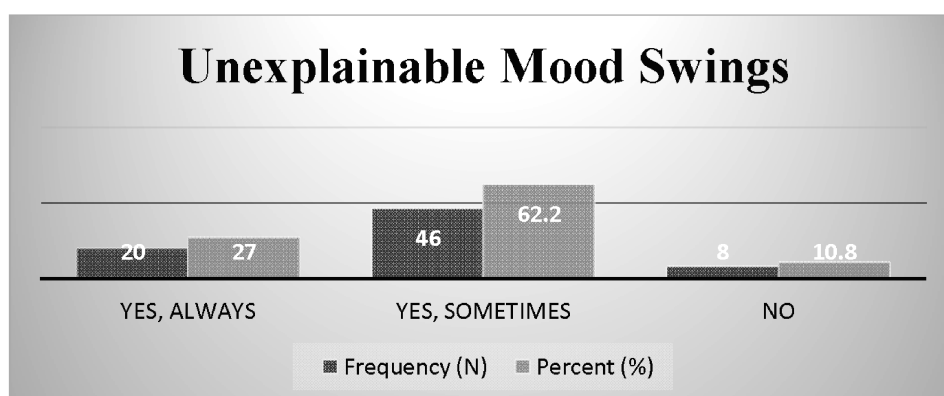


Figure 6 shows the prevalence of unexplainable mood swings. The table shows that amongst the study population 27% females always have unexplainable mood swings, 62.2% sometimes have unexplainable mood swings whereas 10.8% do not have unexplainable mood swings.

7. Distribution of Excess Hair loss or Thinning of Hair in the Study Population (N=74)

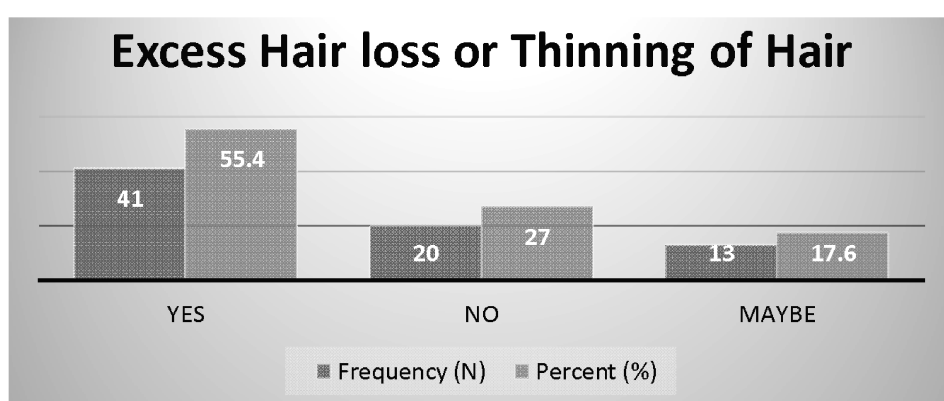


Figure 7 shows the prevalence of excessive hair loss or hair thinning. The table shows that amongst the study population 55.4% females always have excessive hair loss or hair thinning, 27% do not have excessive hair loss or hair thinning whereas 17.6% are not sure.

8. Distribution of Feelings of being Fatigue, mostly in the Study Population (N=74)

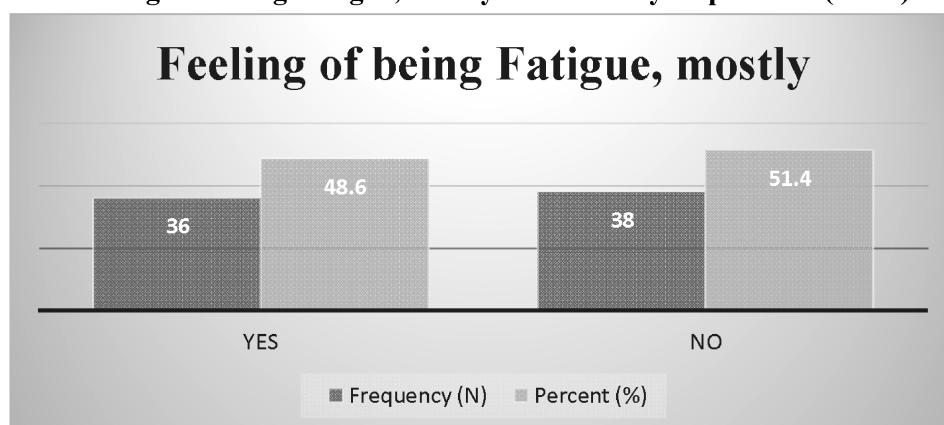


Figure 8 shows the prevalence of mostly experiencing fatigue. The table shows that amongst the study population 48.6% females feel fatigued mostly whereas 51.4% do not feel fatigued.

9. Distribution of Altered Menstrual Cycle Length in the Study Population (N=74)

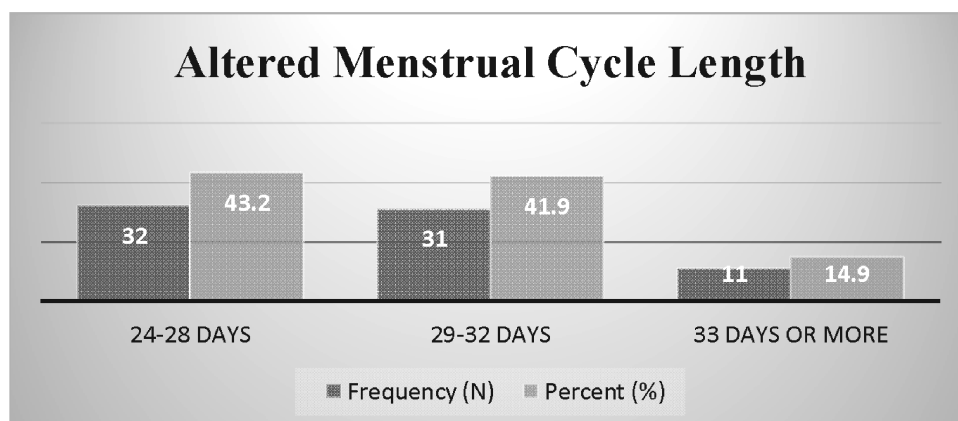


Figure 9 shows the prevalence of altered menstrual cycle. The table shows that amongst the study population 14.9% have cycle length of 33 days or more and 49.1% have cycle length of 29-32 days whereas 14.9% have an altered menstrual cycle of 33 days or more.

Discussion

PCOS being a hormonal disorder has been associated with a number of symptoms [5]. In the present study various symptoms of polycystic ovary syndrome are present in the study population in varying proportions. 14.9% females have irregular menstrual cycle among the participants, 28.4% females have experienced sudden weight gain, 48.6% females have experienced trouble to lose weight, 40.5% females have acne problems whereas 27% experience acne problems sometimes, 28.4% females have experience excessive body hair growth, 27% females always have unexplainable mood swings & 62.2% sometimes have unexplainable mood swings, 55.4% females always have excessive hair loss or hair thinning, 48.6% females feel fatigued mostly and 14.9% have an altered menstrual cycle of 33 days or more.

Conclusion

Polycystic ovarian syndrome is a hormonal disorder that is common in females who are in the reproductive age group. There are a number of factors that have been associated with PCOS like diet, lifestyle, circadian cycle, etc. The prevalence of the symptoms of PCOS has been evidently found in the study population in varying proportions. To have a better understanding of the present scenario and prevalence of the symptoms are needed to be studied in a larger population size.

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Photosensitive Activity of *Curcuma longa* — An Alternative Approach to Antibiotic Resistance

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Abstract :

Resistance to antibiotics is an alarming issue worldwide. Scientists round the globe are becoming extremely cautious and concerned while finding out ways to combat the situation where synthetic antibiotics are gaining resistance. Last few years have witnessed several antibiotic resistances in addition to multi-drug resistance to deadly bacterial infections. Seeking novel approaches to battle multi-drug resistant bacteria have therefore become more and more significant. Incorporating the photosensitive approach involves the use of light-sensitive agents, which are usually nontoxic dyes, as an alternative approach to handle the antibacterial resistance. Numerous studies reveal that natural product, turmeric or *Curcuma longa* prevents the growth of gram-positive and gram-negative bacteria, equally. Pharmaceutical preparations of this herb in nanoparticles, liposome, micelles and other novel formulations have experimentally seen to reduce the intrinsic hydrophobic nature of curcumin, thereby increasing solubility. Several evidences support the augmentation of antimicrobial activity and anti-biofilm activities of curcumin silica nanoparticles against *P. aeruginosa* and *S. aureus* cultures using this pathway. This therapy exhibits significant antimicrobial activity against both strains of bacteria. This review provides an updated information regarding the use of natural products to limit or prevent microbial resistance through use of photosensitizing agent, curcumin.

Keywords : photosensitive, antimicrobial, *Curcuma longa*, nanoparticles, oxygen-free radicals

Introduction

Handling antimicrobial resistance is one of the top-most challenges of the 21st century. It has emerged as one of the foremost fears to public health. World Health Organization (WHO) revealed that infections caused by resistant bacteria affect more than 2 million people and cause more than 20 thousand deaths in the United States and the European Union annually¹. For some 30 years, no new antibiotics have been discovered whilst existing ones fail to suppress or kill the target microorganisms. As a matter of fact, infection by resistant strains drastically reduces the probability of an effective treatment and elevates not only the morbidity and mortality of common infections but also increases the associated health costs, which reach billions per year. All throughout the last decade, WHO has been warning that the post-antibiotic era, where common infections can kill again, is an increasingly real threat². The pace with which the bacterial resistance continues to rise is much higher than the rate of new antibiotics development during the past three decades, with no significant therapeutic class discovered since the 1980's³.

Moreover, extensive use of conventional antimicrobials (antibiotics and antifungals) has seen a significant rise in the problem of microbial resistance, resulting in treatment failure, persistence of infection in addition to other side-effects of drugs especially when multiple antibiotics are used⁴. Owing to these limitations of the currently available drug treatments, antimicrobial alternatives are widely sought for¹. To address such discrepancies, photosensitive activity of certain organic or herbal drugs, frequently referred as antimicrobial Photodynamic Therapy (aPDT), is a promising therapeutic modality. Here, for microbial inactivation, the use of association of a photosensitizing agent (PS) [e.g., curcumin (CUR)] with light at a suitable wavelength⁵ is common. When

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aPDT is active, the interaction between PS and light in the presence of oxygen results in the production of a reactive species, mainly the singlet oxygen and free radicals that promote cell damage and death⁶.

The way in which an *in vitro* study is done and the way bacteria exists in a human being while causing an infection is quite different. Generally, bacteria exist in structured biofilm ecosystems while residing in a human body and rarely in cultures of single species that are traditionally used by microbiologists to study the behaviour of micro-organisms *in vitro*. As a matter of fact, in biofilms, microorganisms are remarkably less susceptible towards antimicrobials as compared to their planktonic complements⁷. The mechanisms of resistance in biofilms include slow diffusion of antimicrobials through the biofilm matrix, changed micro-environment, different stress reaction of bacterial cells, and the formation of a sub-population of so-called persisted cells⁸. Since biofilm infections are a result of diversity of microbial species, potential resistances within the biofilm can easily be transferred among different species by horizontal gene transfer⁹. There is an estimate that more than 60% of all microbial infections are caused by biofilms. In hospital-acquired infections too, this results from compromised sterile conditions. Common biofilm oriented infections include dermal infections, middle-ear infections, urinary tract infections, dental infections (caused by dental plaque), endocarditis and implant- or catheter- associated infections, some of which can lead to lethal consequences for patients¹⁰.

In recent years, photodynamic therapy has come up as a non-invasive therapeutic modality for the treatment of various infections by fungi, bacteria, and viruses. Photodynamic therapy involves an oxygen-dependent photochemical reaction. In this, a photosensitizing compound is instigated by light, leading to the generation of cytotoxic reactive oxygen species, chiefly singlet oxygen¹¹. Superficially, this can be applied to a periodontal pocket, with much lesser associated side effects compared to systemic antimicrobial agent¹². As a result, it can minimize the occurrence of bacterial resistance. Thus, antimicrobial Photodynamic Therapy (aPDT) is an alternate way for antibacterial, antifungal, and antiviral treatment against drug resistant organism, also called as photodynamic antimicrobial chemotherapy¹³.

Numerous studies reveal that curcumin presented remarkable anti-inflammatory, antioxidant, and anticancer activities¹⁴. Recently, researchers have been trying to explore its activity against several bacterial strains¹⁵. However, curcumin suffers from water solubility, instability at physiological pH and low bioavailability¹⁶. It has been demonstrated that polymeric nanoparticles exhibited a remarkable capability to encapsulate curcumin and enhance its therapeutic effects.

Curcuma longa offers curcumin (extracted from the rhizomes of turmeric), a naturally occurring yellow dye, which has been used for more than 4,000 years in traditional Asian and African medicine for the treatment of a variety of ailments¹⁷. This analysis is an attempt to provide a systemic study of the use of aPDT of curcumin in lessening of microbial resistance.

Economic Implications of Antimicrobial Resistance

Curcumin is a cheap ingredient used in cooking in many of the third world countries since time immemorial. It also has a well-established safety profile. Naturally, the focus has been shifted to this commonly available item to counteract the daunting threat of antibiotic threat. Several surveys in developing countries have shown increase in the growth of antimicrobial resistance¹⁸. Figure 1 indicates an emerging group of antibiotic resistant bacteria in human, year-wise. Common man is also becoming careful, like it has drawn the attention of health stakeholders, fitness experts, and medical science due to the substantial economic loss that it can cause to individuals and country as a whole. Appropriate use of antibiotics in treatment, and increased implementation of herbal therapy comes as a ray of hope in combating this threat.

Development of Antimicrobial Photodynamic Therapy

Antimicrobial photodynamic therapy (aPDT) had been proposed to combat clinically related biofilms such as ventilator associated pneumonia, chronic wound infections, dental biofilms, chronic rhinosinusitis, and oral candidiasis. In this approach, aPDT uses non-toxic dyes called photosensitizers (PS), which can be excited by

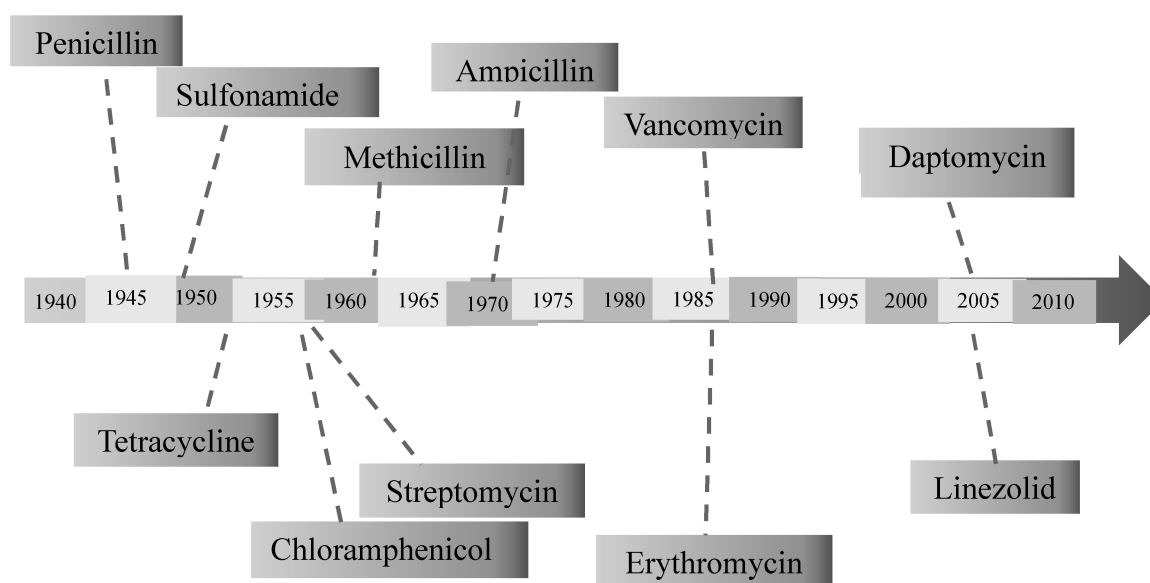


Figure 1 : Antibiotic Resistance Spectrum

harmless visible light to produce reactive oxygen species (ROS). It is a multi-stage process. The stages include topical photosensitizing agent administration, light irradiation, and interaction of the excited state with ambient oxygen. A study divulged that when cells are protected within the microbial biofilms, they become much less sensitive to antibiotics. However, the reactive oxygen species (ROS) generated due to photo activation can destroy the biofilm structure (protein, lipids and nucleic acids) and robs the cells of this protection. This non-specific attack by the ROS can cause overall destruction of both planktonic cells as well as biofilms¹⁹.

Cusicanqui *et al.* developed microcosm biofilms using bovine serum and immersed in McBain medium with 1% sucrose at 37° C for a period of 5 days. They assessed the survival rate by analysing lactic acid concentration. The outcome of curcumin module was noted on overall effect of the microorganism on biofilm after analysing with blue LED at λ_{max} of 455 nm²⁰. Decreased viability of infecting cells in dental caries was noted. In another study to reduce antibiotic resistance of *Staphylococcus bacteria*, curcumin encapsulated PLGA nanoparticles were used. The ability to selectively activate curcumin nanoparticles with low-energy LED light to eradicate *Staphylococcus saprophyticus* was successfully demonstrated. In a similar study, when chitosan was used to augment the induced surface charge, increased photo-dynamic penetration ability⁴ was noted. So it appears that encapsulation in nanoparticles improves the water solubility of curcumin, and thereby potentiated its effect.

Conclusion

It can be concluded from this study that curcumin mediated antimicrobial photodynamic therapy (aPDT) minimises viability of several antibiotics resistant microorganism. The potency of curcumin can be increased manifold by designing the dosage form in novel formulations surpassing the water insolubility issue of curcumin thereby elevating the bioavailability. In absence of new antibiotics, aPDT is a smart way to handle the issue of antibiotics resistance.

Acknowledgment

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Conflict of Interest

The authors do not hold any conflict of interest.

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West Bardhaman district's preparedness to deal with oxygen surge during 2nd wave of covid-19: a case study

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Abstract :

Covid 19 was declared a pandemic in Mid-March 2020. Ministry of Health and Family Welfare had geared up to combat the oxygen surge in all the states since the inception of pandemic. The projected oxygen requirement was made on the assumption that since Covid 19 Virus belongs to coronaviridae family. Previous other disease caused by virus in the family were severe acute respiratory syndrome and Middle East Respiratory Syndrome occurring almost in the same period. In a hospital ward there are ways of oxygen delivery during the fall in patient's oxygen saturation. Some provide intermittent oxygen supply some provide continuous supply. The present study has been undertaken to assess the health system delivery in West Bardhaman district, to assess the preparedness of the health system to tackle the problem of oxygen surge during the rapid rise of Covid 19 cases. During the period of March to July 2021. It has been a narrative review based from the services provider's statements It describes regarding the number of beds with continuous oxygen supply and description of devices present to provide continuous oxygen supply. There appears to be some lacunae to tackle the oxygen surge. However, with decline of 2nd wave requirement also decreased. Now since in 3rd wave no surge in oxygen demand or requirement for hospital bed was observed. Preparation made may have fallen into disuse. If the system is prepared to be tackle against a future epidemic/pandemic a detailed study has to be carried out.

Key words - Covid 19, Oxygen Surge, West Bardhaman District, Mutation, 2nd wave

Introduction

West Bardhaman is one of the 23 districts in West Bengal. District Headquarters is Asansol, the city is second to Kolkata in terms of population and area[1]. Covid 19 outbreak 1st case in West Bengal was reported 17th March 2020 as per newspaper report [2]. Since the inception of pandemic in India the various DO letter had asked the state governments to beef up the health facilities in terms of oxygen supply and bed strength [3]. The reasons for this assumption was that etiological agent for Covid 18 is SARS- COV2 belongs to class of virus known as Coronaviridae. The same family of virus which was responsible for severe acute respiratory syndrome (SARS) and Middle East Respiratory syndrome (MERS). Those two viral diseases that is SARS and MERS disappeared abruptly. This was because it had a very high case fatality rate. SARS had a case fatality rate was around 10% and MERS was around 34%. So, risk of transmission was low. The cases of Covid 19 have a long incubation period with a low fatality rate. There are sub clinical infection and symptomatic infections. The risk of transmission is higher particularly during the incubation period It is in backdrop of risk of transmission and risk of sudden surge of oxygen requirement there was a felt need of increased requirement of oxygen and oxygen supported beds.

Requirement for oxygen to deal with oxygen surge was felt more during the during the 2nd wave. SARS CoV2 is the 7th viral infection belonging to CoV family. Mutation in the structure of genome sequences and also ability of the virus penetrates cells and affection of the respiratory tract and ability to cause acute respiratory illness.

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It would remain a cause concern for the future and as well as the viral genome to escape immunity provided by the presently used Covid Vaccine [4]. The 2nd wave of the Covid 19 across pan India, occurred during the month of March through July 2021. If one analyzes the lay news reports of the period, it shows a sudden surge of cases requiring oxygen. Since the cases surged like wave in a sea hence called of 2nd wave [5]. In anticipation of the possible surge the state government had already mobilized development partners to tackle the projected scenario. During the surge industrial oxygen was diverted for supply medical needs. The case fatality rate, exact numbers mortality the death due to Covid 19 varied for of each of the state and country. Data is difficult to obtain. However, the data provided by WHO estimates and government data was vastly different (6).

Provision of oxygen in case of Covid 19, Managing Covid Cases – types of hospital beds requirement

Oxygen requirement for any admitted cases is provided through Mobile oxygen cylinder or short intermittent oxygen supply generation from room air (oxygen concentrator). These means are inadequate oxygen surge during Covid 19 acute pandemic. Such temporary requirement oxygen was possible in Safe Homes (Covid Care Center) or in isolation homes. More prolonged requirement of oxygen in a hospital is supplied through central oxygen pipe line system. Ministry of Health and Family Welfare have classified Covid Care facilities into 3 types based on the oxygen requirement. In a facility where there is no oxygen requirement or oxygen can be supplied through portable oxygen cylinder is called Covid Care Center or in West Bengal was called as safe home. Dedicated Covid Care Health Hospital and Dedicated Covid Hospital has been established to deal with oxygen surge. In such facilities was provided with Pressure Swing Absorption plants or Liquid Oxygen plants or have the provision for oxygen supply [7].

Methodology

This present study is a narrative review The data was obtained after discussion with the service provider and officials of the development partner who were involved in the process of strengthening oxygen supply in public facilities.

Results and Findings

Beyond July 2021 when the 2nd wave had abated in West Bardhaman district.

Total number of beds which were allocated for Covid treatment are

Present beds with oxygen support	Beds without oxygen support	Planned for future
606	502	0

Table 2- Beds at the July 2021 and projections for future waves in West Bardhaman district

Current Liquid (Liquid Medical Oxygen) in with buffer stock requirement	0
Future Liquid Medical Oxygen in buffer stock requirement	0
Current Pressure Swing absorption plant capacity	0
Future Pressure Swing abortion plant capacity	2000
Medical Gas Pipeline supplied present beds	360
Medical Gas Pipeline supplied future beds planned	0

Discussion

Data shows the oxygen requirement as has been obtained from reliable sources shows requirement was adequate

to tide over oxygen surge. The 3rd wave caused by Omicron variant of SARS CoV 2 showed sudden rise and a fall. Hospitalization was not that required too. However, the months of April and May 2021, was indeed a challenging time. Critical interventionist toiled hard. Health facilities were overburdened on a daily basis with a large number of cases. The cases that reached hospital showed signs of respiratory distress. It is to be noted that statement issued by statutory body of critical interventionist, how to deal with critical cases. Liquid Medical Oxygen, compressed oxygen cylinders are recognized sources of oxygen facilities. They should be used judiciously. More focus should be given to noninvasive methods of oxygen supply. There were plans made for boosting the requirement.

Now as the 2nd wave abated the urge for the strengthening also abated. The 3rd wave which was in January 2022 showed no trend of a surge. Oxygen requirement remained normal Hence the plan which had been put up in place in 2020 through 2021 has been fallen through probably because of other priorities for the government. It can also be inferred that as most of the population are vaccinated worst is possibly behind us, until there is a massive surge of breakthrough infection [7].

Conclusion

Therefore, infrastructure which had been put in place in West Bardhaman district to deal with the possible surge of oxygen requirement in wave of Covid 19 could be best described probably as a onetime affair. If these facilities are still maintained or ready to use cannot be ascertained for sure, because it would require monitoring and evaluation. This would be an expensive issue without adequate funding and hence cannot be undertaken without financial support and administrative approval.

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Factors responsible for treatment deviation in tuberculosis patients in India

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ABSTRACT

Claiming the lives of 1.5 million people each year, Tuberculosis is one of the most infectious diseases worldwide. India being the highest TB burden country still fails to control it despite implementation of RNTCP. It suffers from shortage of diagnostic facilities, drug supplies, trained personnel and inadequate management of treatment. Moreover, one of the major problems is the large number of people who either refrain from treatment initiation or default. Therefore, this review is conducted with an aim to understand the various factors influencing delay in treatment initiation and reasons behind non-adherence.

Several databases like PubMed, Google Scholar, Scopus etc. were systematically searched to identify studies published during 2010-2020 that were relevant to the research topic. The findings were analyzed and synthesized in a narrative style using the thematic synthesis approach.

Several socio-demographic, socio-cultural, patient-related and service provider related factors were highlighted. Some of the main factors responsible for delay in initiation and non-compliance to the treatment were: low literacy level, lack of awareness about severity of the disease and importance of treatment completion, low SES, migration, lack of family support, social stigma, side-effects of ATT drugs, distance of the health facility, inadequate patient provider interaction etc.

The policy makers should strategize new programs and strengthen the existing ones by focusing on staff training regarding information dissemination, screening of patients, counselling to decrease default rates. Efforts should also be made to increase awareness and literacy levels among people to understand the gravity of the situation and to comply with the treatment and support the providers trying to help them.

Keywords : tuberculosis, treatment deviation, health policy, India, ATT drugs.

INTRODUCTION

Tuberculosis (TB) is a highly contagious bacterial infection caused by acid-fast bacilli *Mycobacterium tuberculosis*. It can affect other parts of the body like intestine, bones and meninges (extra pulmonary TB) but predominantly affects the lungs (pulmonary TB) [1]. From public health point of view pulmonary TB especially sputum smear positive cases are more important as they can transmit the disease to others through air/droplet nuclei. The disease progresses fast in immune compromised states, most commonly with HIV/AIDS. Recent evidence suggests that in 2019, globally 10.4 million people contracted the disease and 1.4 million were reported dead including 208,000 among HIV patients [2]. India, being amongst one of the highest TB burdened countries has 40% of its population infected. In 2015, an estimated 2.2 million incident and 2.5 million prevalent cases were recorded in India [3]. The financial implications of TB on Indian economy are huge amounting to roughly 3 billion USD with a huge loss in terms of lives, money and workdays. In 1993, WHO declared TB as a global emergency and since then intensive efforts have been made to control the disease worldwide [4].

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In India, Revised National Tuberculosis Control Program (RNTCP) based on Directly Observed Treatment Short Course Strategy (DOTS) of WHO was launched in 1997 [5] and gradually implemented to achieve nationwide coverage in March 2006 [3]. Despite achieving the set targets of 70% case detection and 85% treatment success rates, TB continues to elude the DOTS program from achieving desired efficiency [6]. With early case detection and diagnosis and prompt initiation of regular anti-tubercular treatment, TB is a treatable and curable disease [4]. One of the major challenges faced by the TB control programs is delayed reporting and defaulting from treatment. Non-compliance to prescribed dosage and poor patient adherence to treatment regimen are responsible for treatment failure and emergence of MDR-TB.

Recent scientific evidence suggests that “the finding of a single AFB in at least one single sputum smear examination in a TB suspect would satisfy the criterion to report a patient as having ‘sputum smear-positive tuberculosis’ and to subsequently start treatment” (WHO, 2012). Emphasis has been given on early diagnosis and treatment initiation of sputum positive pulmonary TB cases and to monitor success in treatment initiation an operational indicator known as ‘Initial Defaulter Rate’ has been kept under RNTCP. Adherence to TB treatment is one of the factors that lead to increase in cure rate. This reduces mortality and emergence of multi drug resistant tuberculosis (MDR) and lowers the high cost of treatment resulting. Tuberculosis does not discriminate on age, sex or education level. Previous research in different contexts has shown that there exist many factors influencing non-compliance. They range from individual patient, health care provider, health care delivery patterns and socio-economic related factors influencing non-adherence to TB treatment [7].

Tuberculosis (TB) is a major contributor to the global burden of disease. Poor adherence to treatment is common despite various interventions aimed at improving treatment completion. Currently, posed is a challenge of non-adherence to treatment despite efforts with patient centered approach which allows home-based treatment supervised by a treatment supporter of their own choice, and health facility-based treatment observed by a health professional.

Lack of a comprehensive and holistic understanding of local and community-based barriers can be a hindrance to achieving success in STOP TB interventions. New infections, TB drug resistance, high treatments costs and mortalities have been associated with non-adherence.

The RNTCP - , defines - , an - initial defaulter , as - , a , diagnosed , TB patient - who , has - , been recorded in the laboratory register, but who has neither been placed - on - , an RNTCP regimen - nor - , been referred - , for , treatment under , the RNTCP outside the district [8]. The RNTCP envisages initiation of TB treatment within seven days of case detection. A primary concern regarding initial default is that they continue transmitting the disease to others. It is therefore of paramount importance to find out the factors responsible for delay in initiation of treatment despite presence and implementation of a well-organized TB control program in India with diagnostic facilities and drugs made freely available across the country. Previous studies [9] have indicated that some of the factors responsible for initial default are chronic cases, lower age group, male sex, travel expenses to treatment centres, alcoholism, homelessness, poor patient awareness and information about the importance of treatment initiation, lack of motivation, poor pre-treatment counselling and DOTS providers belonging to government sector. These factors may be different for different states and districts across the country. Those not initiating and defaulting from treatment after getting diagnosed are not only a threat to themselves but also to others in their proximity as they are the one responsible for spreading the disease and perpetuating the infectious cycle which could have easily been treated and prevented by just complying with the treatment regimen. Adherence to TB treatment is one of the factors that lead to increase in cure rate. This reduces mortality and emergence of multi drug resistant tuberculosis (MDR) and lowers the high cost of treatment resulting.

Lack of a comprehensive and holistic understanding of local and community based barriers can be a hindrance to achieving success in STOP TB interventions. New infections, TB drug resistance, high treatments costs and mortalities have been associated with non-adherence. If no efforts are put to determine the factors locally influencing non-adherence, the STOP TB programs will continue using strategies that are standardized, which might not yield effective results as per the context. Also the local and national tuberculosis burden will be on

the increase in terms of Multi-Drug Resistance (MDR), mortality and treatment cost. Therefore, this study aims to explore the reasons pertaining to non-initiation of treatment and causes of default among NSP cases.

REVIEW OF LITERATURE

In India, in the year 2019, the total population covered under RNTCP was 21.5 lakhs. Out of this approximately over 9 lakh smear positive cases were diagnosed. Over 14 lakh patients were registered for treatment. However, high default rates among diagnosed cases or non-initiation of treatment after being diagnosed were reported to be an area of concern. India accounts as the highest TB burden country in the world with 26.9 lakh incident cases reported worldwide [5]. Despite DOTS being available and accessible to more than a billion people in India, more than 30% of states still report a cure rate of less than 85% and a default rate of more than 5% [10]. Defaulting from treatment, non-compliance to anti-tubercular regimen along with non-initiation of treatment in new sputum positive cases remain the major obstacles to treatment management and an important challenge for TB control. The public health impact and clinical repercussions of treatment defaulter or those who do not initiate treatment after getting diagnosed are alarming. Therefore knowledge of the drivers of treatment default is essential for successful TB control and optimal delivery of healthcare services in resource poor settings like India [11]. Certain studies have found out that high risk of treatment default exists in those with an HIV-TB co-infection and in those with an unknown HIV status as compared to ones who are HIV negative. Several studies conducted among HIV-TB co-infected patients have cited social stigma and anticipated fear of high pill burden and intolerability to the strict regimen of both anti-retroviral along with anti-tubercular drugs as one of the main reasons for initial default and non-compliance [12].

Several studies have found the major reasons for non-initiation of treatment was lack of awareness about the severity of TB, improper patient provider interaction, inadequate patient counselling, alcoholism and long distance of DOTS centre from their residences [13]. The association of alcohol consumption and default has also been emphasized by a study conducted by [15]. Another study conducted by Ahmed et al., 2020 highlighted lack of follow-up of newly diagnosed sputum positive cases and infrequent home visits by health care providers as the major cause of non-initiation of anti-tubercular treatment (ATT). Inaccessibility to healthcare services and lack of knowledge regarding risks and consequences of non-initiation and non-completion of ATT were major reasons elicited in a similar study conducted in Indonesia [14]. Several studies have found population migration and perceived side-effects of anti-tubercular drugs to be relevant reasons for non-compliance and default [15,16]. Certain studies have reported forgetfulness of patients to go DOTS clinic and take medicines as one of the reasons for default. Evidence suggests that maximum default was encountered during the intensive phase of treatment or right after the patients were diagnosed due to unstable living conditions and lack of social support to go through with the treatment.

METHODOLOGY

RESEARCH DESIGN AND RATIONALE :

A narrative review methodology with a systematic approach was chosen as the study design for carrying out this project work. A narrative review formulates a comprehensive study by combining all the findings and evidences from various studies. It also provides for an in-depth exploration of the available literature on a topic and helps to address theoretical questions that are way beyond the scope of a single primary study [17]. Therefore to acquire a comprehensive understanding of the factors responsible for non-initiation of treatment in diagnosed smear positive pulmonary TB patients, a narrative review methodology was considered more apt.

As this study focuses on exploring the human behaviour and aims to investigate the reasons responsible for the pattern of compliance exhibited by different individuals towards anti-tubercular treatment offered, a narrative review seems more pertinent as it can justify broad conclusions about human nature, behaviour or human condition as opposed to a single empirical study. Moreover, adopting a narrative review methodology to address this research question will ensure that a holistic perspective is being used to ascertain various barriers to starting of therapy in diagnosed TB cases. Also, the existing literature and evidence from previous studies on the topic

compound a heterogeneous base and India is a diverse country with huge inter-state variations.

DATA SOURCES AND SEARCH STRATEGY :

Electronic databases such as Pubmed, Web of Science, Google Scholar, Scopus etc. were meticulously searched. These databases contain relevant medical and health science related information suitable for carrying out this review.

INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA :

Studies available in English language. Studies conducted from the year 2010 till 2020, studies that have explored reasons for non-initiation of treatment or non-adherence to treatment among diagnosed pulmonary TB patients. Studies published on diagnosed sputum positive pulmonary TB patients in India.

EXCLUSION CRITERIA:

Studies not published in English language and those published before 2010 will be excluded. Studies focusing on issues of extra pulmonary TB patients. Studies on patients in general which do not hold any relevance to the selected research topic and studies on pulmonary TB patients who do not live in India have not been included in this review.

DATA EXTRACTION AND ANALYSIS:

After thoroughly reviewing the selected studies, pertinent information related to the research topic from each study extracted and presented in tabular form. This tabular representation helps in summarizing all the information reviewed in each study, along with highlighting the main findings of the studies thus providing a systematic overview and clear understanding of the existing literature on the topic.

ETHICAL CONSIDERATION:

As this dissertation is a narrative review based on existing literature and previously conducted studies and does not involve any human participation, an ethical approval was not deemed necessary.

RESULTS AND FINDINGS

A total of 13 studies were selected for conducting this review. Some of the studies included in this review were qualitative and others were cross-sectional quantitative studies. The findings of the reviewed papers were they analysed using a thematic approach and presented in narrative synthesis style. Several factors influencing the behaviour and approach of patient's adherence to ATT regimen were identified after reviewing the studies and were then grouped together to generate major theme and sub-themes. The four major themes that were identified are: socio-demographic factors, socio-cultural factors, patient-related factors and service provider related factors.

AGE

Majority of non-adherent patients were reported to be in the age group 15-49 years. Some of the reasons for default may be forgetfulness to take the pill and lack of social support from family and friends and also failure to understand instructions given by the health care workers, However, further research needs to be done to understand the effects of age on adherence to tuberculosis treatment.

GENDER

In comparison to females, males were found to be more non-compliant to treatment regimen. Various studies carried out in other countries also indicate that male were more likely to default from treatment. One of the

reasons for this pattern was men spending more time on their jobs trying to earn their livelihood which made it difficult for them to devote time towards visiting a treatment facility and adhering to the prescribed regime.

EDUCATION

Higher educational status is expected to reflect good knowledge of TB and also more earning power, which in turn may affect compliance. Education overall increases knowledge and health awareness and treatment seeking behavior of the individual. Literate individuals are more likely to complete the treatment. We observed that patients who have completed at least high school education were strictly treatment adherent. We noted decrease in trend of non-adherence as level of education increased.

OCCUPATION/EMPLOYMENT

Many studies report association of unemployment and non-adherence. But, we found that some studies document unemployed patients were more treatment adherent. It may be due to time available to go to DOTS centre to take doses on proper time. Also, females contributed majority of unemployed group and as discussed earlier females are more treatment adherent. On the other hand males who were unemployed or those belonging to a low socio-economic strata were found to be more non-adherent as they would mostly migrate to different areas away from their homes in search of better job opportunities. for various employment opportunities. TB patients domiciled at treatment place used to be more treatment adherent than migrants. Migration may force them to live alone or without family, to get minimal social support and to live in overcrowded and unhygienic environment. Daily wage earners have higher risk of not keeping appointments at the clinic especially if work place is not nearby.

FAMILY TYPE AND SUPPORT

Lack of family and social support leads to poor treatment adherence. In our study, patients not living with own family were observed to leave the treatment halfway as compared to patients living with family.

STIGMA

TB-associated stigma often in our society plays an important role in abstaining patients from seeking early health care due to fear of being diagnosed with TB and recognised. It is difficult to quantify stigma but being stigmatized by the family, society or the providers or just the fear of being stigmatized can lead to non-compliance if the system never allows flexibility.

RELIGION

Some studies have documented the reason for default was also religious belief and myths of patient's that offering prayers and deities could cure them of the disease rather than relying and complying with the western medicines.

ALCOHOL CONSUMPTION AND SMOKING

Alcoholism has been identified as an important predictor of noncompliance in several studies. As, smoking is most of the times associated with alcoholism, it can also predict poor treatment adherence. Additionally, drug or alcohol use increased the duration of hospitalizations. Missed appointments were also associated with alcohol and drug use [18].

DIET

Most of the patients believed that for one to experience fewer side effects and tolerate his or her drugs well must have an adequate diet, and lack or no food at all would lead to very severe side effects and failure to tolerate the anti TB drugs. The majority of patients, most especially those who had insufficient income frequently

mentioned lack of food as a factor that greatly influenced their adherence to TB treatment, it could be better for someone without food not to take drugs at all as drugs can be harmful on an empty stomach, and also that TB drugs increase appetite and after taking them one would feel hungry and yet food is already a problem ¹². Patients with little or no food end up not taking their TB treatment as prescribed for fear of an increased appetite or the adverse effects of the drug associated with lack of food leading to either non adherence or poor adherence to TB treatment.

FEAR OF SIDE-EFFECTS

Presence of severe to moderate side effects may cause cessation of drug intake for a while until some interventions are made and the side effects are brought to bearable limits. On the other hand, a clear explanation of the possible side effects is made initially and this helps to comply better. Frequently reported minor side effects could be successfully dealt with proper instructions on drug consumption, reassurance to patients and prompt symptomatic treatment before it leads to default.

LACK OF AWARENESS

Lack of adequate knowledge about the severity of TB and the importance of regular ATT intake was another barrier in adherence. Some patients were found to have defaulted owing to having assumed to be cured as they felt better some days after treatment initiation.

ATTITUDE/BEHAVIOR OF THE SERVICE PROVIDERS

Evidence suggests that judgmental attitude, unsupportive behaviour and lack of interest of service providers negatively influences the patient's desire to initiate or continue with the treatment regimen. Dissatisfaction with treatment services and poor patient provider interaction were apparent determinants of default and barriers in utilization of services.

DIFFICULTY IN ACCESSING HEALTH FACILITY

Distance to the health facility is a major factor for compliance. For want to keep the diagnosis a secret some people prefer distant health facility but for some it is difficult to travel daily to longer distances to take the anti-tubercular drugs under the supervision of a DOTS provider. The additional cost of transportation and long waiting hours without being attended to at most health centers has refrained them from accessing such facilities.

INCOMPETENCE OF THE DOTS PROVIDERS

Shortage of staffs at the health facilities, lack of adequate training of the RNTCP staff in interpersonal communication skills needed to motivate and deal with TB patients all have been perceived as hindrances in optimal service delivery. RNTCP staff should screen all TB patients for factors predicting possible non-adherence since at the time of diagnosis and treatment initiation. Patients with such risk factor should be motivated to follow DOTS through counselling. Trained counsellors are needed to be appointed to counsel cases having a cock-tail combination of risk factors for non-adherence.

DISCUSSION OF FINDINGS

Based on the findings of this review, the major factors identified that influence treatment initiation and encourage treatment default in diagnosed pulmonary TB patients are socio-demographic factors, socio-cultural factors, patient related factors and provider related factors. Certain studies highlight socio-demographic factors such as age and sex of the patient to be more influential in deciding adherence to treatment whereas other studies have shown socio-cultural factors such as lack of family support and social stigma as major obstacles in patient's compliance towards anti-tubercular treatment. Some authors have documented provider related factors such as inadequate patient-provider interactions, lack of knowledge of the DOTS provider regarding the importance of

treatment completion and inadequacy on their part to follow-up patients to be the most important factor creating hindrance to treatment initiation and adherence. However, this review basically focuses to explore the factors responsible for delay in treatment initiation and compliance of patients to the ATT regimen which are essentially largely a behavioural pattern affected by a complex interaction of all the above mentioned factors.

Several policies and programs (RNTCP, DOTS) launched and implemented by the Govt. of India for service provision to TB patients are functional but still a gap exists between the level of service provision and the degree of utilisation. Several reasons behind this existing loophole in the system have been explored and highlighted in the studies included. They are age, gender, illiteracy, lack of proper knowledge regarding importance of treatment completion and the consequences of default, social stigma associated with the disease, lack of family support, frequent migration in search of employment, fear of side-effects of the anti-tubercular drugs, unhealthy habits like smoking and alcohol consumption, distance of the treatment centre, difficulty in accessing the services and unsupportive attitude of the service providers.

STRENGTHS OF THE REVIEW

By choosing a details systematic search strategy I have included as much studies relevant to the research topic in order to make the review representable. The study included in this review are conducted in different parts of the country and published over a period of 10years, it can reasonably be concluded the research based for this review is extensive the findings can be easily transferable. Most of the studies included in this review are case-control, qualitative studies which are appropriate for studying and estimating the behavioral pattern of the population.

RECOMMENDATIONS FOR SERVICE PROVIDERS

Study identified many loopholes in supervision of ATT under DOTS given by private practitioners. Effective mechanisms have to be evolved to ensure treatment adherence through PPP (public-private-partnership) approach. There is immense need for continuous, effective and reinforcing health education to the patient and his family. Treatment providers should pay special attention to male patients in 15-49 year age group, from lower SES, migrants, habitual smokers, alcoholics. Special groups who do not have any family support like FSWs, migrated individuals living alone or without family need special attention and provisions under RNTCP, at least in study area. Training of RNTCP staff in interpersonal communication skills is needed to be enhanced to deal with TB patients. They should be adequately trained to disseminate correct knowledge about TB disease and its treatment to the TB patients. They should also be adequately trained and supervised about strict adherence to transferring out procedures.

All patients should be thoroughly screened for any factors predicting possible non-adherence since at the time of diagnosis and treatment initiation. Patients with such risk factor should be motivated to follow DOTS through counselling. Trained counsellors are needed to be appointed to counsel cases having a cock-tail combination of risk factors for non-adherence. It should be done with the help of relatives and/or person who has positive impact on patient's behavior.

CONCLUSION

The most commonly cited reason for default was migration. Synthesizing the findings, the overall factors found to be independently associated with default were consumption of alcohol, unsatisfactory knowledge about TB, inadequate patient provider interaction, instances of missed doses, adverse reactions of anti-TB drugs, attitudes of the government DOT providers, and smoking habits of the patients. During pre-treatment counselling information regarding duration of treatment, importance of treatment completion, adverse effect of drugs etc needed to be emphasized to the patients. Also, patients using alcohol need to be kept under strict monitoring and should be given repeated counselling. This study showed that inadequate general knowledge on TB, loss of employment, stigma and lack of social support, medication side-effects and long treatment period posed as barriers to effective treatment adherence. The short distance to reach health facilities and good communication and positive attitude

of health care providers towards their patients were found to be enablers to treatment adherence. For better treatment adherence, comprehensive health education at treatment sites, involvement of patient's family members and the community at large and strengthening of social support structures need to be addressed.

To decrease non-adherence rates and to improve treatment outcome of TB-patients, healthcare professionals, health policymakers and other stakeholders should give emphasis to prevention of co-morbidities, improving knowledge through health education, providing strong counselling about drug adherence with more emphasis on continuation phase of treatment and about disadvantages of alcohol intake, and strengthening of patient-provider relationship. Non-adherence is associated with the risk factors that are modifiable by the correction of socio-demographic and economic characteristics as a whole. So, the highest priority in fighting against non-adherence therefore must be to reduce poverty for its alleviation especially targets the patients of low economic status.

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Beneficial effects of lemon (*C.limon*)

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Abstract :

This review presents the importance of lemon fruit or *C.limon* for human health. Lemons are very nutritious and have many medicinal properties. Lemons are available almost whole year and not much costly so lemons are used as medicinal plant from ancient period. In ancient period lemons are used in treatment of scurvy as it is rich in ascorbic acid/vitamin C. Lemon contains high amounts of vitamins and minerals with polyphenols, flavonoids, carboxylic acid and the most important compound D-limonene present in the essential oil obtained from peel. For this rich nutrient and chemical compound content, lemon has many significant biological activities which are health beneficial. The therapeutic activity of lemon are antioxidant activity (by radicle scavenging), anticancer activity (by inhibiting cancer cell proliferation, inducing apoptosis of cancer cell), anti-inflammatory activity, antiallergic activity, antimicrobial activity (antibacterial, antifungal, antiviral), cardioprotective activity (reduces high blood pressure, treats hyperlipidemia), antidiabetic activity (reduces high blood sugar and insulin resistance), increasing gastric motility, relieves gastric reflux, Hepatoregenerating activity, prevention of anemia etc. Besides the pharmaceutical uses lemons are also used in food industries, cosmetic industries and biotechnological studies.

Keywords : Lemon, blood sugar, therapeutic activity

INTRODUCTION

From ancient period different types of herbal medicines are used to treat different types of disease in undeveloped, developing and advanced countries as they have less side effects. Those countries are the natural origin of herbal/medicinal plants. There are around 21,000 medicinal plants enlisted by World Health Organization (WHO) [1]. Citrus are one of the important medicinal plant genus under the *Rutaecae* family. There are approximately 130 genes and 1400 species of citrus genus. Lemon are one of the most popular citrus fruit throughout the world which is multifunctional, beneficial for health and have great nutritional property (nutrient content). The scientific name of lemon is *Citrus limon* [2]. Lemon belongs to the evergreen tiny flowering tree also known as 'four seasons' as it produces fruits and flower whole year.

Lemon has multiple medicinal properties. it is used as the remedy for scurvy and is used as a traditional medicine or Ayurveda. It has anticancer effect and antimicrobial (antibacterial, antiviral, antifungal) activities. It also has Anti-diabetic, antioxidant/cardioprotective, hepato-regenerating, anti-inflammatory and anti-ulcer activity. in traditional medicine it is used in the treatment of high blood pressure, common cold and cough, irregular menstruation, sore throats, fevers, chest pain rheumatism, arthritis, respiratory problems etc. Lemon also helps to prevent kidney stones. [2-4].

History and Origin:

The term or name 'lemon' has come from the ancient French word 'limon'. In different languages it has different names-lemon in English, Zitronen in German, le citron in French, limón in Spanish, and níngmèng, in Chinese, nimbu in Hindi, lebu in Bengali etc. [2] In 2000AD lemon plant was first cultivated in Southern Italy and then it was taken to Iraq, Egypt and Persia in 700 AD. In between 1000-1150 AD lemon tree was distributed

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throughout the Mediterranean region and Arab. Lemon tree was cultivated in China during 760-1297 AD. In 1493, Christopher Columbus brought Hispaniola lemon seeds and introduce them in North America. In 19th century California and Florida starts cultivation of lemon tree. In 1747, James Lind first discovers that lemon has an important role in cure of scurvy.[9]

Lemon is native to the north east India. It is believed that lemon was first cultivated in the Assam, northern Burma or China. Currently, USA, Italy, Turkey, Israel, Spain, Argentina, Brazil and Greece are the larger producer of lemon. In India, the main lemon producing states are Andhra Pradesh, Bihar, Gujarat, Maharashtra, Rajasthan, and Tamil Nadu. [1]

Dry climate and low rainfall are the best condition for the growth of lemon, but can also grows in heavy rainfall. High humidity, frost, salt water, hot air wind is dangerous to the lemon tree. The best time for lemon tree is between June to August. [1]

Taxonomical Classification: [5]

Kingdom: Plantae

Subkingdom: Angiosperms

Phylum: Eudicots

Class: Rosids

Order: Sapindales

Family: Rutaceae

Genus: Citrus

Species: *C. limon*

According to the studies university of California lemon or *C. limon* is the combination of 2 species *C. aurantium* (bitter orange) and *C. medica* (citron) and the studies of Southwest university of China has proved that *C. limon* is the hybrid of *C. aurantium* and *C. medica*. [10]

Description:

Lemon fruits are round or oval in shape with a broad, low, apical nipple (in oval) and have 8-10 segments [11]. Lemons are generally greenish yellow in color but when lemon ripe and grows in size became bright yellow. The peel is thick in some varieties and is dotted with oil glands. The white spongy part of the peel is known as mesocarp or albedo which is tasteless and is the main source of commercial pectin. In one lemon there are about 8-10 seeds known as floopies. The seeds are small, ovoid and pointed. lemon has sour, astringent taste and the pulp is acidic in nature. [11]

Nutrient and chemical composition:

The main raw material of the lemon is the fruit, particularly the essential oil obtained from it which is rich in nutrient content. Lemon is the one of the important, richest source of vitamin C/Ascorbic acid. Also contains many vitamins, minerals, flavonoids, polyphenols, phenolic acid, carboxylic acid etc. The important chemical compound of the essential oil are monoterpenoids, especially D-limonene. Rich chemical content of lemon gives it importance in food, drug and cosmetic industries. [6-8]

Importance for health

1. Antioxidant activity:

Lemon is one of the most important sources of antioxidants as it contains richer amount of vitamin C/ascorbic acid, flavonoids and phenolic compounds. Also, lemons contain carotenoids, glutathione and other enzymes

system which also have significant role in antioxidant activity. The antioxidant activity of flavonoids-hesperidin and hesperetin present in lemon has free-radical scavenging activity, excites the antioxidant cellular defences via the ERK/Nrf2 signalling pathway, prevents formation of free radicals, protects DNA from mutation.[12]

2. Anticancer activity:

Lemon contains vitamin C, folate and other bioactive components, such as carotenoids and flavonoids responsible for prevention of cancer and other degenerative disease by their anticancer activities. The compounds present in the aqueous extract of fruit protects the body cells from the damage caused by cancer. So, lemon is used in anti-angiogenic therapy and cancer controlling.[13] The nanovesicles present in lemon extract-inhibits the cancer cell proliferation in different tumour cell line with the help of 'TRAIL' (TNF related apoptosis-inducing ligand) mediated apoptotic cell death, inhibits the tumour growth in chronic myeloid leukaemia (CML)[14]. 80:20 methanol: water extract of lemon seed induces apoptosis in human breast adenocarcinoma (MCF-7) cell which leads to inhibition of proliferation.[15]

3. Antimicrobial activity:

Lemon extract and the essential oil have shown inhibiting activity against many bacteria. For e.g gram positive bacteria such as *Enterococcus faecalis* and *Bacillus subtilis* and gram-negative bacteria such as *Salmonella typhimurium*, *Shigella sonnei*, *Helicobacter pylori*. [16,17] Lemon extract has important role as antifungal and antiviral activity. Lemon extract inhibits the activity of fungus such as *Aspergillus niger*, *Saccharomyces cerevisiae*, *Candida parapsilosis* strains (D-limonene, α -pinene, citral) [18] and activity of virus such as *Herpes simplex* [19]

4. Anti-inflammatory activity:

The lemon extract has a significant role as anti-inflammatory. The anti-inflammatory activity of lemon are-inhibiting cell migration, inhibition of cytokine production, inhibition of inflammatory mediator leukocyte chemotaxis (D-limonene),interacting with the 5-lipoxygenase, TNF- α (tumour necrosis factor), IL-6(interleukin-6), inhibiting NF- κ B factor, nitric oxide (II) synthase (iNOS), inducing cyclooxygenase (COX-2) (hesperidin, hesperitin), Down-regulation of TLR-signaling pathway (limonin).[20]

5. Antiallergic effect:

According to the investigation aqueous extract from lemon peel inhibits histamine secretion from rat peritoneal exudate cells (PECs) by the calcium ionophore A23187.[21]

6. Antidiabetic effect :

According to the studies lemon extract has an important role in preventing diabetes and to treat their symptoms. Lemon peel extract contains high amounts of polyphenols which reduces the high blood glucose and insulin resistance [22]. To reduce blood glucose lemon extract inhibits gluconeogenesis. lemon extract also reduces wound healing time, increases the tissue growth rate, collagen synthesis and protein and hydroxyproline concentration.[23]

7. Cardioprotective effect and anemia prevention:

Lemon juice and walking together helps to reduce blood pressure in hypertensive patients as both have negative correlation with the systolic blood pressure. Lemon extract reduces the naringenin or myocardial damage.[24] lemon juice decreases blood fibrinogen and thus prevents clotting.[25] As lemon juice is richer source of ascorbic acid, it helps in iron absorption and thus prevents anemia.

8. Effect on digestive system:

D-limonene present in the essential oil of lemon peel increases gastric motility, neutralizes stomach acids, reliefs

gastric reflux and reduces nausea.[26]

9. Hepatoregenerating effect:

Ethanol extract of lemon normalize the aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase (ALP), and total direct bilirubin level in liver damage induced by carbon tetrachloride (CCl₄). It also reduces the malonic dialdehyde (MDA), lipid peroxidation, superoxide dismutase (SOD) and catalase [27]. In chronic liver poisoning lemon essential oil detoxifies the liver by the activation of cytochrome P₄₅₀ and liver enzymes (glutathione S-transferase).[28]

10. Effect on lipid profile:

Lemon extract helps in lowering cholesterol levels by decreasing triglyceride and LDL level and increasing the HDL level. It reduces the cholesterol and arachidonic acid level by stimulating liver enzymes and cytochrome. In order to maintain normal blood lipid levels it have lipolytic effect (α-terpinene and p-cymene) [29].

11. Effect on nervous system:

Helps in Strengthening short-term memory, D-limonene has inhibiting effect on pain receptors like indomethacin and hyoscine (D-limonene). It also has sedative and anxiolytic effect by activating serotonin and dopamine receptors.[30]

Conclusion

At the end of the review article we can conclude that *C.limon* is a wonder fruit. Lemon juice, extract, pulp, essential oil obtained from peel are very much health beneficial. Every product of lemons are rich in nutrient and chemicals which are important for many biological activities. Flavonoids, polyphenols, D-limonone etc are present in lemon which are responsible for antioxidant, anticancer, anti-inflammatory activities etc.

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Relationship between diet and mental health

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ABSTRACT

While our mood drives our cravings and the sort of nourishment we choose, food greatly affects how we feel. Emotions have an impact on eating, but food's nutritional qualities have an effect on brain processes associated to mood and sentiments. The brain, like every other organ, is fostered by nutrients found in the food. As a result, the nutritional properties of food have an effect on brain activities associated with mood and emotion. Specific nutrients can help treat certain emotional and mental illnesses, and nutritional deficiencies have been shown to have a harmful influence on mental sanity. Many are aware of the link between poor nutrition and physical sickness, however only few people are aware of the link between nutrition and depression. Depression is more frequently regarded as having purely physiological or emotional roots. Contrarily, diet can have a significant impact on the onset, intensity, and course of depression. A growing field called nutritional neuroscience is shedding insight on how nutrition affects human brain, behavior, and emotions. The average population's food intake pattern in many Asian and American nations shows that they are frequently low in numerous nutrients, including vital vitamins, minerals, and omega-3 fatty acids. The degree of deficit in these essential nutrients is a noticeable aspect of the diets of people suffering from mental illnesses like depression, bipolar disorder, schizophrenia, obsessive-compulsive disorder (OCD). Paying closer attention to our everyday diet and consuming the essential nutrients in the right proportions may improve our mood.

Keywords : Depression, Nutrition; Mood; Diet; Polyunsaturated fatty acids; Glycemic Index ; Essential Amino Acids; Neurotransmitter

INTRODUCTION

We need to pay attention to how our mental health affects our eating choices as much as how food affects our mood. Emotions do impact food choices. Food and mood interact in a cycle that must be understood in order to effectively manage mental health[1]. The food affects the mood, which in turn affects the food choices that ultimately enhance or worsen the disposition. There is now a tons of data that suggests what we eat on a daily basis might affect our mood as a result of research into the relationship between food and depression. According to research, a healthy eating regimen, such a Mediterranean diet, can benefit mental health. This contains a variety of lean meats, fish, and dairy products in moderation along with lots of fruits, vegetables, nuts, seeds, and olive oil. A healthy diet also avoids added sugar, trans fats, and saturated fats, all of which have been linked to heart disease and obesity. Also a healthy diet is rich in antioxidants and fibre.[2]

Numerous studies have been conducted on the negative impact of mood on food consumption. The urge to eat and the amount of food ingested were both favourably and adversely correlated with mood. Some studies suggest the role of various nutrients, like vitamins, minerals, and antioxidants[2]. These theories emphasize on the part that these micronutrients play an important role in proper functioning of human body. Other studies examine the significance of the gut microbiome—the collection of microorganisms that lives in the gut, and how the foods we eat affect it. The diverse bacterial and microbiota that live in the gut. Eatables can influence this microbiota.

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GUT BRAIN AXIS - The enteric and central nervous systems are connected by a bidirectional communication network called the gut-brain axis. In addition to being anatomical, this network also includes endocrine, humoral, metabolic, and immunological pathways for communication.[3] The brain may regulate intestinal processes, including the activation of functional immune effector cells, through the autonomic nervous system, hypothalamic-pituitary-adrenal (HPA) axis, and nerves in the gastrointestinal tract, whereas the gut can affect mood, cognition, and mental health. In contrast to GI illness, which frequently involves psychological comorbidities linked to altered gut flora, various mood disorders, including anxiety, depression, and autism spectrum disorders, now have well-established linkages to functional GI disturbances.[2]

CARBOHYDRATES

Carbohydrates are naturally occurring polysaccharides that play a significant part in an organism's structure and function. Carbohydrates have an influence on person's mood and behavior. Eating a carbohydrate-rich meal causes the release of insulin in the body, which facilitates the entrance of blood sugar into cells where it is utilized for energy while also triggering the entry of tryptophan into the brain. The levels of neurotransmitters in the brain are affected by tryptophan. Low carbohydrate diets tend to cause sadness because carbohydrate-rich meals stimulate the creation of brain chemicals serotonin and tryptophan, which increase feelings of well-being. Also, foods low in GI such as various fruits – apples, orange and vegetables – cucumber, tomatoes, spinach; whole grains; are more likely to have a modest but long-lasting influence on brain chemistry, mood, and energy level than high GI foods such as white rice, white bread, mangoes, watermelon, ice cream, sweets etc which tend to give quick but short comfort [1]. Serotonin (or 5-hydroxytryptamine; 5-HT) is synthesised from the precursor essential amino acid tryptophan (TRP) in the presence of an enzyme called tryptophan hydroxylase, which converts TRP to 5-hydroxytryptamine. 5-HT has long been implicated in sleep and emotional disorders such as sadness and anxiety. Serotonin and tryptophan have been shown to improve mood. These brain chemicals' production (5-HT and TRP) is triggered by carbohydrate-rich foods.[3]

PROTEINS

Every human body cell contains important proteins that are important for the formation of DNA, hormone production, growth, and the building of muscles and tissues. They are vital for the anabolic process, recovery, maintaining a healthy body weight or loss, and lowering the danger of cardiovascular risk. Proteins function in the human body in ways that are in addition to their basic physiologic functions. Proteins are amino acid-based and are essential building blocks of life. There are 20 amino acids which are produced by the body and are therefore known as Non Essential Amino acids, while the remaining 8 amino acids have to be supplied via diet and are known as Essential Amino acids.[1] People who suffer from severe depression should consume more protein and high-protein foods. High-protein soy snacks have been shown to improve mood and cognitive function in adolescents, as well as their ability to regulate their appetite and feel full. A high quality protein diet such as milk, egg, meat, fish etc contains all the EAA. Plant proteins like beans, peas, and grains are deficient in one or two important amino acids. Protein consumption, and hence specific amino acids, can have an impact on brain function and mental wellness. Many neurotransmitters in the brain are composed of amino acids. The amino acid tyrosine is used to make the neurotransmitter dopamine, whereas tryptophan is used to make the neurotransmitter serotonin. If any of these two amino acids is deficient, there will be insufficient synthesis of the corresponding neurotransmitters, which is related with poor mood and aggressiveness behavior.[1] Tryptophan-containing foods raise serotonin levels in the brain and affect neuronal processing in mood-regulating neurocircuits. However, tryptophan competes for transport across the blood-brain barrier with other large-neutral-amino-acids (LNAA), a constraint that can be overcome by boosting the tryptophan/LNAA ratio. The LNAA include tyrosine, threonine, methionine, valine, isoleucine, leucine, histidine and phenylalanine.[3] Conversely even excessive amino acid accumulation can potentially cause brain damage and mental impairment. For example excess phenylalanine accumulation causes phenylketonuria which can induce brain damage and mental retardation.[1]

VEGETABLES AND FRUITS – Fruits and vegetables are categorised as foods containing micronutrients, which include trace minerals and water-soluble vitamins associated with health and wellbeing. Additionally, they contain significant levels of phytochemicals that have anti-oxidant, anti-bacterial, and anti-mutagenic properties. Eating unprocessed fruits and vegetables is associated with better mental health. Increased vegetable and fruit eating has been linked to healthy mental health, cognition, and mood in both men and women because of their high nutritional content. Consumption of colourful fruits and vegetables on a regular basis by young adults was linked to happier moods, higher levels of creativity and curiosity, and other traits that are favourable to pleasure. Consuming flavonoids, which are present in fruits and vegetables, is suggested by epidemiologic research to be linked to a lower incidence of depression. Flavonoids reduce depression-causing cognitive processes and raise mood via enhancing executive function associated with cognitive processes.

WATER -Water is the most important component of life since it is necessary for every single living cell to operate and thrive. Additionally, it aids in the production of saliva, controls body temperature, safeguards organs and tissues, aids in the elimination of waste products through sweat, urine, and faeces; helps in digestion and physical performance, and prevents constipation and dehydration. Additionally, it aids in food absorption, weight reduction, blood oxygenation, combating infections, increasing energy, and enhancing mood. Mood is eventually impacted by inadequate water intake. Women who didn't drink enough water were more likely to have mood disorders including despair, anxiety, and aggression. However, these mood-related symptoms had a favourable or negative impact on how much water was consumed during the day. Fluid deprivation is associated with dehydration, which leads to fatigue, alertness, decreased activity, decreased saliva roduction, and poor sleep quality. Armstrong et al. found that bad mood highly correlated with lower water in-take.

ESSENTIAL FATTY ACIDS -The brain is a fat-rich organ, with phospholipids, sphingolipids, and cholesterol found in the lipidic brain membrane.[3] The grey matter of the brain contains 50% polyunsaturated fatty acids (PUFA), 33% of which belong to the omega-3 family. Clinical and epidemiologic research show that a lack of dietary n-3 polyunsaturated fatty acids (PUFA) may raise the risk of numerous mental diseases, including depression. N-3 PUFAs - DHA and EPA - reduce inflammation by modifying the intensity and duration of the inflammatory response. Thus, n-3 PUFAs may contribute to antidepressant benefits and/or resistance to depression via anti-inflammatory pathways. DHA is the most abundant PUFA in the brain, accounting for roughly 15% of total fatty acids in that region. Endogenous synthesis of these long-chain PUFAs occurs from -linolenic acid and eicosapentaenoic acid. DHA and arachidonic acid (omega 6) cannot be produced by animals and must be obtained through food.[1]

MICRONUTRIENTS

The most prevalent sign of folate insufficiency is depression. Depression patients have 25% lower blood folate (B9) levels than healthy persons. Vitamins B6 and B12, among others, have a direct role in the creation of some neurotransmitters. Cobalamin (B12) supplementation increases cerebral and cognitive abilities while also preserving the integrity of the nerve fiber's myelin sheath. Zinc, folic acid, magnesium, vitamin C, and vitamin B12 have been shown to alleviate depressive symptoms. These nutrients, which may be obtained from asparagus, beets, peas, beans, chickpeas, soybeans, lentils, cabbage, spinach, broccoli, pumpkin seeds, almonds, barley, and mushrooms, have been reported to increase mood via their function in the synthesis of neurotransmitters.[4]

- The rich sources of serotonin include tomato, banana, pineapple, plum and kiwi, while for melatonin fenugreek seeds, white and black mustard seeds. Citrus fragrances are famous for their mood enhancing properties, volatile oils segregated from grapefruit (C. Paradisi), lemon (C. lemon), bergamot (C. bergamia), lime (C. aurantifolia), mandarin (C. nobilis) and orange (C. aurantium) are often used for treating anxiety.[4]
- Honey is commonly utilised for its medicinal effects. Fructose, glucose, amino acids, vitamins, minerals, and enzymes are among the 200 elements found in it. Honey has been shown to significantly decrease anxiety and strengthen motor function in rats. This might be because honey contains the crucial

avonoidchrysin, and chrysin has also been shown to ameliorate cognitive deficits and brain damage caused by chronic cerebral hypoperfusion in rats.[4]

LINK BETWEEN FOOD, MOOD AND DISEASE

DIABETES -Diabetes and food are closely associated. Healthy food choices and sound eating practises are advantageous for people with diabetes mellitus. Mood can adversely affect insulin resistance as well. Depression symptoms and a negative mood raise blood sugar levels in diabetes individuals. For individuals with long-standing diabetes mellitus and young women in particular, a low mood can considerably raise sugar levels. Worse consequences including poor glycemic control, diabetic foot syndrome, severe hypoglycemia, coma, renal failure, stroke, and other diabetic obstacles are brought on by this impact. Additionally, food addiction and cravings are important causes of the increased incidence of obesity. The presence of diabetes and glycemic management are impacted by high BMI.[5]

OBESITY -Obesity (BMI 30 kg/m²) has raised concerns worldwide and is linked to a number of health issues, as well as rising mortality and morbidity rates. According to studies, obesity is strongly related to food intake and food craving. Dopamine activates pleasure centres in the brain when it is released by the body when a person is satiated after eating. In order to have this sensation of fulfilment, this will encourage someone to repeatedly eat particular foods, which ultimately promotes binge eating and severe obesity. Additionally, mood changes and emotional eating may affect the foods people choose to eat and the amount they consume, which can lead to obesity. Therefore, abnormal eating habits and mood disorders are linked. Depression and anxiety are more frequently present when a person is obese. Obesity has been linked to damage to or incapacity of the central nervous system, which has a detrimental effect on both mental and physical health.[5]

DEPRESSION - A condition that affects how we feel is depression. In contrast to a physical injury or disease, it may take time to manifest and we may not always be able to detect it just by looking at someone. This is because depression has an impact on the brain regions that manage our emotions.[2] Depression is a sort of mental disorder, which are illnesses that affect our feelings, thoughts, and actions. Both depression and emotional eating influence food choices and increase the consumption of unhealthy foods. Depressed individuals who engage in emotional eating tend to eat more sweet foods while depressed individuals who do not engage in emotional eating consume less fruits and vegetables. Consuming comfort foods heavy in fat and sugar, including desserts and fried meals, boosts mood by stimulating the reward centres of the brain.[5]

FOODS THAT CAN BOOST MOOD

CAFFEINE - Caffeine is seen as a national drug that has the potential to greatly affect everyday mood and mental health. It function as a central nervous system stimulator may momentarily increase activity. In habitual caffeine users, temporary caffeine shortage causes withdrawal symptoms. Caffeine use in the morning has been shown to dramatically lessen morning stress and improve performance. It has been proven to significantly reduce tiredness and boost alertness. Consuming caffeine at various times and in various dosages can drastically affect mood, and modify behaviour. It has been reported that those who consume coffee regularly have a lower incidence of depression. Numerous negative side effects from consuming too much coffee include tension, nervousness, anxiety, headaches, and sleeplessness. Some researchers recommended decreasing caffeine intake since they did not discover any appreciable benefits of caffeine on mood elevation.[5]

CHOCOLATE - According to studies, eating sweets and other delectable meals improves mood, with a stronger effect on women than on men. Chocolate has a strong effect on mood, frequently evoking positive emotions and reducing stress. Chocolate contains psychoactive chemicals that target the opioid receptors in the central nervous system (e.g., anandamides), which act at the same site in the brain as cannabis and tyramine and phenylethylamine, which act similarly to amphetamine, making it a popular choice as an anti-depressive agent. Chocolate also contains theobromine and caffeine, which are known to have stimulant properties. High-quality chocolate

consumption elevates mood and increases daytime alertness. After 3 days of chocolate consumption, significant improvements in mood and decreased exhaustion had been noted. Due to its outstanding flavour and tongue feel, chocolate makes people crave it after eating. However, consuming these items in excess has a detrimental impact on the consumer since it makes them lose control and devour sweets. Over time, excessive chocolate intake has been linked to higher levels of anxiety than moderate to low consumption.[5]

CONCLUSION

It may have sounded ‘mood uplifting’ to know that anti-depressants need not be used and yet depression can be rooted out. While food and diet are well known to improve or deteriorate physical conditions, it is only logical that the psychological health is also affected by what we eat, especially by what is missing from our nourishment. The food we eat affects our mood - Our diets play a crucial role in both maintaining our physical and emotional health. This implies that nutrition may be able to play a significant role in the prevention and treatment of one of the most prevalent mental health diseases in the world i.e. depression.

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A review on Nutraceuticals classification and its role in various diseases

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ABSTRACT

Nutraceutical is the hybrid of 'nutrition' and 'pharmaceutical'. Nutraceutical in broad sense are food or part of food playing a significant role in modifying and maintaining normal physiological function that maintains healthy human beings. The principle reasons for the growth of the nutraceutical market worldwide are because of the population and health trend. The food products used as nutraceuticals can be categorized as dietary fibre, prebiotics, probiotics, polyunsaturated fatty acids, antioxidants and other different types of herbal or natural foods. These help in combating major health problems of the century such as obesity, cardiovascular disease, cancer, osteoporosis, arthritis, diabetes, cholesterol etc. The concept of nutraceuticals started from a survey in U.K, Germany and France which found out that diet is rated more highly by consumers than exercise or hereditary factors for achieving good health. By adding nutraceuticals, it may be possible to reduce or eliminate the need for conventional medications, reducing the chances of any adverse effect. With a global increase in the prevalence of obesity, both nutrition and exercise play key roles in prevention and treatment. Using food products to promote health and cure disease is renowned. Currently most of the drug molecules available in the formulations were anciently used in their crude form. Nutraceuticals are obtained from vegetal or animal origin food and prospective research on them will clarify their role, safety, and efficacy. In whole, nutraceutical has led to the new era of medicine and health and has become research oriented sector.

Keywords: Dietary Fibre, Diseases and Treatment, Polyphenols, Human diet, Prebiotics, Probiotics, PUFA, Antioxidants

INTRODUCTION

The term nutraceutical was coined from 'nutrition' and 'pharmaceutical' in 1989 by DeFelice and was originally defined "as a food that provides medical or health benefits".[1] A nutraceutical may be a naturally nutrient-rich food such as spirulina, garlic, soy or a specific component of a food like omega-3 oil from salmon. They are also known as medical foods, nutritional supplements and dietary supplements. It ranges from isolated nutrients, dietary supplements, generally engineered "designer" foods, herbal products, and processed products such as cereals and soups. They have received considerable interest because of their presumed safety and potential nutritional and therapeutic effects. The role of dietary active compounds in human nutrition is one of the most important areas of investigations with the findings having wide-range implications for consumers, healthcare providers, regulators and industry [1]. Food and nutrition plays an important role in reducing various risk of diseases and worldwide acceptance of this fact formed a recognition link between nutrition and health and thus the concept of nutraceuticals evolved.

Classification of Nutraceuticals

The food sources used as nutraceuticals are all natural and can be categorized as :

1. Dietary Fiber

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2. Probiotics
3. Prebiotics
4. PUFA
5. Antioxidant vitamins
6. Polyphenols
7. Spices [1]

ABOUT NUTRACEUTICALS

Dietary Fiber

It consists of non-digestible carbohydrates and lignins that are intrinsic and intact in plants. Functional fiber consists of isolated non-digestible carbohydrates that have beneficial physiological effects on human health. Total fiber is the sum of the dietary and functional fiber. The adequate intake for fiber defined by the Dietary Reference Intake (DRI) is 38grams/day for the adults men and 25grams/day for adult women.[2]

Probiotics and Prebiotics

These are good for human health especially for gut health. Our body is full of both good and bad bacteria where probiotics are called good bacteria and these are naturally present in our body.

- A. Lactobacillus – Most common probiotics found in yogurt and fermented foods. Different strains can help with diarrhea and may help people with lactose intolerance.
- B. Bifidobacterium – This is also found in dairy products and it ease the symptoms of IBS and some other conditions. Researchers are still trying to figure out the conditions and health problems. Some conditions are :
 - IBS
 - IBD
 - Diarrhea
 - Anti-biotic related diarrhea
 - Eczema
 - Urinary and vaginal health
 - Preventing allergies and cold
 - Oral health

Prebiotics are substances that induce the growth or activity of microorganism examples are bacteria and fungi that contribute to the well-being of their host. The most common example is GI tract, where prebiotics can alter the composition of organisms in the gut microbiome. For example, certain hand moisturizers have been proposed to act like prebiotics to improve the activity or composition of skin microbiota.[2]

In diet prebiotics are typically non-digestible, fiber compounds that pass undigested through the upper part of the GI tract and stimulate the growth or activity of advantageous bacteria that colonize the large bowel by acting as substrate for them [2]. As a functional food component, prebiotics like probiotics are conceptually intermediate between foods and drugs. Although all prebiotics are fiber, not all fiber is prebiotic. Classification of a food ingredient as prebiotic requires scientific demonstration[2]

- Resists gastric acidity, hydrolysis by mammalian enzymes, and absorption in the upper GI tract
- Fermented by intestinal microflora
- Selectively stimulates the growth or activity of intestinal bacteria potentially associated with health and well-being.

Some of the health benefits are :

- Reduce prevalence and duration of infectious and anti-biotic associated diseases.
- Exert protective effects to prevent colon cancer
- Enhance the bioavailability and uptake of minerals including calcium, magnesium, and possibly iron.
- Lower some risk factors for CVD and,
- Promote satiety and weight loss and prevent obesity.

Polyunsaturated fatty acids (PUFA)

The group of PUFAs is divided into two groups: omega-3(n-3) and omega-6(n-6) polyunsaturated fatty acids differing in the position where the first double C bond is located. One is linoleic acid belongs to n-6 family. The other one is linolenic acid belongs to n-3 family. These essential parent compounds can be converted in the human body to long chain fatty acids but humans cannot interconvert n-3 and n-6 fatty acids.

Antioxidants

Antioxidants are our first line of defense against free radical damage, and are critical for maintaining optimum health and wellbeing. Antioxidants are capable of stabilizing, or deactivating, free radicals before they attack cells. Antioxidants are absolutely critical for maintaining optimal cellular and systemic health and well-being. Humans have evolved a highly sophisticated and complex antioxidant protection system. It involves a variety of components, both endogenous and exogenous in origin, that function interactively and synergistically to neutralize free radicals. These components includes :—

- Nutrient-derived antioxidants like ascorbic acid (vitamin C), tocopherols and tocotrienols (vitamin E), carotenoids and other low molecular weight compounds such as glutathione and lipoic acid.
- Antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and glutathione reductase, which catalyze free radical quenching reaction.
- Numerous other antioxidants phytonutrients present in plant food.

Endogenous antioxidants

- Bilirubin
- Thiols, eg, glutathione, lipoic acid, N-acetyl cysteine
- NADPH and NADH
- Ubiquinone (coenzyme Q10)
- Uric acid

Enzymes :

- Copper/zinc and manganese-dependent superoxide

- Iron-depleted catalase
- Selenium-dependent glutathione peroxidase[3]

Dietary Antioxidants

- Vitamin C
- Vitamin E
- Beta carotene and other carotenoids and oxycarotenoids
- Lycopene and lutein
- Polyphenols, eg, flavonoids, flavons, flavonols
- Proanthocyanidins

Metal Binding Proteins

- Albumin (copper)
- Ceruloplasmin (copper)
- Metallothionein (copper)
- Ferritin (iron)
- Myoglobin (iron)
- Transferrin (iron)

Polyphenols are natural phytochemicals compounds in plant-based foods, such as fruits, vegetables, whole grains, cereals, legumes, tea, coffee, wine and cocoa, where there is more than 8000 polyphenolic compounds including phenolic acids, flavonoids, stilbenes [3], lignans, and polymeric lignans have been identified in whole plant foods. Polyphenols are classified into several categories based on the number of phenol rings and structural elements that binds these rings to one another [3]

Phenolic acids are approximately a third of the polyphenolic compounds in the diet and include two main classes:

1. Hydroxybenzoic acid derivatives (protocatechuic acid, gallic acid, p-hydroxybenzoic acid) and
2. Hydroxycinnamic acid derivatives (caffeic acid, chlorogenic acid, coumaric acid, ferulic acid, sinapic acid), berry fruits, apple, pear, cherry, kiwi, coffee are the foods with high content of these phenolic acids.

There are six subclasses of flavonoids including anthocyanins, flavonols, flavanols, flavonones, flavones, isoflavones found in berries family, red wine, red cabbage, cherry, black grape, and strawberry.

Spices

Spices have been virtually indispensable in the culinary art of flavoring foods since antiquity. Spices are aromatic vegetable substances, in whole, broken or ground form, whose significant function in food is seasoning rather than nutrition. These spices give flavor, aroma and pungency to food. Volatile oil spices responsible for aroma, flavor and oleoresin contribute the pungency. Spices are also used rather widely used in indigenous medicines, pharmaceuticals, Nutraceuticals, aroma therapy, preservatives, beverages, natural colors, perfumes, dental preparations, cosmetics and botanicals as pesticides and thus, play a significant role in the economy of the producing country. These properties are due to diverse array of chemicals synthesized by these spices. Growing demand from the emerging segment of

nutraceuticals is driving the global consumptions of Indian spices further to meet the needs of traditional food sector.

Chawanprash is one of the highest marketing nutraceutical product in India. It contains spice ingredients like cinnamon, clove, curcuma spp, saffron and long pepper. As these are good sources of vitamin C and rich in antioxidants which helps in increasing immunity, increase digestion and prevents cough, asthma, fever, heart disease, impotency and coarseness speech. Spices like turmeric, red pepper, black pepper, ginger, garlic, coriander, rosemary, saffron and cinnamon has been shown to exert its activities against neurodegenerative diseases [3].

The concept of beauty and cosmetics is an ancient as mankind and civilization. Herbs and spices have been used in maintaining and enhancing human beauty since time immemorial. For example turmeric is used for skin care. The anti-ageing and cosmeceuticals is gaining importance in the beauty, health, and wellness sector. Application of turmeric extract cream (0.5%) regulates sebum in human skin, person with excessive oily skin or suffering from acne will have great benefit from this property. Saffron as complexion promoter in skin care and reported that 0.3% of saffron used in cream and lotion will be giving brighter and shiny skin, this effect is mainly due to the crocin and crocogin content of saffron that regulates the melanin biosynthesis of skin.[3]

IMPORTANCE OF NUTRACEUTICALS IN TREATING DIFFERENT DISEASES

1. Cardiovascular Diseases (CVD)

Antioxidants, Dietary fibers, Omega-3 Polyunsaturated fatty acids, Vitamins, minerals for prevention and treatment of CVD. Polyphenols in grapes prevent and control arterial diseases Flavonoids in onion, vegetables, grapes, red wine, apples, cherries block the ACE and strengthen the tiny capillaries that carry oxygen and essential nutrients to all cells. Rice bran lowers the serum cholesterol levels in blood, lowers the level of LDL and increases the level HDL in cardiovascular health. Higher the ratio will be the risk of coronary heart diseases. Rice bran contains both Lutein and Zeaxanthin, which improves eyesight and reduces the chance of cataracts. The essential fatty acids, omega-3, omega-6, omega-9 and folic acid in rice bran are also promoting eye health. It is reported that low intake of fruits and vegetables is associated with a high mortality in CVD. [4]

2. Diet Related Diseases

In Western societies, the incidence of diet-related diseases is increasing due to greater consumption of hyper caloric die/food and following sedentary lifestyle. Obesity, diabetes, atherosclerosis, and neurodegeneration are major diet-related pathologies that share a common pathogenic denominator of low-grade inflammation. Functional foods and nutraceuticals may represent a novel therapeutic approach to prevent or attenuate diet-related diseases in view of their ability to exert anti-inflammatory responses. In particular, activation of intestinal T regulatory cells and homeostatic regulation of the gut microbiota have the potential to reduce low-grade inflammation in diet related diseases.[4]

3. Heart attack and lung cancer

Corn's contribution to heart health lies not just in its fiber, but in the significant amounts of folate that corn supplies. Corn maintains the homocystein, an intermediate product is an important metabolic process called the methylation cycle. Homocystein is directly responsible for damage of blood vessels heart attack, stroke, or peripheral vascular disease. It has been estimated that consumption of 100% of the daily value (DV) of folate would reduce the number of heart attacks suffered by 10%. Corn also contains cryptoxanthin, a natural carotenoid pigment. It has been found that cryptoxanthin can reduce the risk of lung cancer of 27% on daily consumption.

4. Diabetes

Ethyl esters of n-3 fatty acids may be beneficial in diabetic patients. Docosahexaenoic acid modulates insulin resistance and is also vital for neurovisual development. Lipoic acid, an antioxidant, for treatment of diabetic neuropathy. Dietary fibers from psyllium have been used for glucose control in diabetic patients and to reduce lipid levels in hyperlipidemia.

5. Obesity

Obesity is a global public health problem and is defined as accumulation of unhealthy amount of body fat. It is a well-established risk factor for many disorders like angina pectoris, congestive heart failure (CHF), hypertension, hyperlipidemia, respiratory disorders, renal vein thrombosis, osteoarthritis, cancer and reduced fertility[4].

6. Cancer

Flavonoids which block the enzymes that produce estrogen reduce estrogen induced cancers. Prevent prostate/breast cancer a broad range of phyto-pharmaceuticals with a claimed hormonal activities, called “phytoestrogens” is recommended. Soyfoods source of isoflavones, curcumin from curry and soya isoflavones posses cancer chemo preventive properties. Lycopene concentrates in the skin, testes, adrenal and prostate where it protects against cancer.

7. Anti-inflammatory activities

Curcumin which is a polyphenol of turmeric possesses anticarcinogenic, antioxidative and anti-inflammatory properties. Top of form beet root, cucumber fruits, spinach, and turmeric rhizomes, were reported to posses anti-tumor activity. Gamma linolenic acid found in green leafy vegetables, nuts, vegetables oils, i.e. evening primrose oil, blackcurrant seed oil and hemp seed oil, and from spirulina cyanobacteria are used for treating problems with inflammation and autoimmune diseases. Glucosamine and chondroitin sulphate are used against osteoarthritis and regulate gene expression and synthesis of PGE₂. Cat's claw acts as a potent anti-inflammatory agents. Cat's claw is a rich source of phytochemicals 17 alkaloids, glycosides, tannins flavonoids, sterol fractions and other compounds.[4]

8. Alzheimer's disease

Beta-carotene, curcumin, lutein, lycopene and turmerin may exert positive effects on specific diseases by neutralizing the negative effects oxidative stress mitochondrial dysfunction, and various forms of neural degeneration.

9. Parkinson's disease

Vitamin E in food may be protective against Parkinson's disease. Canadian researchers indicated that vitamin E in food may be protective against Parkinson's disease. Creatine appeared to modify Parkinson's disease features as measured by a decline in the clinical signs [4]. Nutritional supplements have shown some promising results in preliminary studies, it is important to remember that there is not sufficient scientific data to recommend them for Parkinson's disease at present. The patients should be cautioned that over-the-counter medications do have side effects and interactions with other drugs and are also expensive.

10. Osteoarthritis

Osteoarthritis a joint disorder is the most common form of arthritis in the United States where it effects as estimated 21 million people. Joint discomfort from OA and other disorders may reduce physical activities in individuals experiencing this condition resulting in energy imbalance and weight

gain. Increased weight can exacerbate existing problems through additional stress on joint [5]. Glucosamine GLN and chondroitin sulfate are widely used to alleviate symptoms of OA. These nutraceuticals have both nutrient and pharmaceutical properties and seem to regulate gene expression and synthesis of NO and PGE2, providing an explanation of anti-inflammatory activities.

11. Adrenal Dysfunction

Adaptogens are natural herbs that have non-specific, normalizing effects on physiology, they influence normal body functions only enough to encourage non-specific resistance to stressors. Adaptogens include herbs Eleutherococcus senticosus, Ocimum sanctum, panax ginseng and mushroom Cordyceps sinensis. Ginkgo biloba has been used for several thousand years by the Chinese for various maladies, including vertigo, short term memory loss and lack of attention or vigilance. Standardized extracts of ginkgo have been shown to possess antioxidant and neuroprotective properties including slowing the progression of dementia.

Ocimum sanctum (holy basil or tulsi) is used in Ayurvedic medicine and has been shown to have antistressor effects. Subjected rats to acute or chronic noise stress, with and without Ocimum administration. Those rats that had been pretreated with Ocimum, whether exposed to acute or chronic noise, had significantly reduced levels of corticosterone.[5]

Some of the benefits of Nutraceuticals :-

- Benefits for physiological effects on human health
- Action on immune system, respiratory and digestive systems
- Limits the use of medicines

NUTRACEUTICALS AND THEIR USES

Chemical constituents	Sources	Use
Carotenoids		
Lycopene	Guava, papaya, water melon, tomatoes, pink color grape fruit	They reduce cholesterol level, antioxidants, protects against cancer
Beta-carotene	Vegetables, fruits, oats, carrots.	Antioxidants protection of cornea against UV light
Lutein	Spinach, corn, avocado, egg yolk activity [6]	Protects eyes against age related muscular degeneration, cataracts, anticancer
Tocotrienol	Palm oil, different grains	Improves cardio vascular health, fight against breast cancer
Saponins	Beans like soya beans, chickpeas reduces cholesterol level	Very effective against colon cancer,
Polyphenolic compounds		
Flavonones	All citrus fruit anticancer activity	Different types of anti-oxidant and
Flavones vegetables	Different types of fruits, soya beans, anticancer activity	Different types of anti-oxidant and

Flavonols	Broccoli, tea, onions, fruits like apple	Antioxidant activities
Curcumin	Turmeric root	Strongly anti-inflammatory and strongly antioxidant effective, anti-clotting agent
Glucosinolates	Cauliflower, cruciferous vegetables bladder cancer [6]	Anticancer activity, protect against
Phytoestrogen		
Isoflavones	Legumes, beans like soy beans	It lowers LDL cholesterol, antioxidants, protects against prostate, breast, bowel and other cancers
Lignans	Vegetables, rye and flaxseeds	Protect against development of cancer like colon and breast cancer
Dietary Fibers		
Soluble fibers	Beans like legumes cereals like oats, barley, some fibrous fruits activity	They help in maintenance of healthy digestive tract and have anticancer
Insoluble fibre	Whole grains food wheat and corn bran nuts activity	They help in maintenance of healthy digestive tract and have anticancer
Sulphides/Thiols	Present in cruciferous vegetables	Maintain healthy immune function
Fatty acids		
Omega 3 fatty acids	Present in salmon and flax seeds	They are the potent controllers of the inflammatory process, help in maintenance of brain function and reduce cholesterol disposition
Monounsaturated fatty acids	Present in tree nuts	Reduce the risk of coronary heart disease
Prebiotics/probiotics	Lactobacilli, bifidobacter present in yogurt and other dairy and non-dairy application	They help to improve GI health and systematic immunity
Minerals like zinc, calcium, selenium, copper, potassium	Food	They are the important constituents of balanced diet
Polyphenols, sugar alcohols	Present in foods	They may reduce the risk of dental cavities [6]

CONCLUSION

Nutraceuticals has proven their health benefits and diseases prevention capability which should be taken according to their acceptable recommended intake. In the present scenario of self-medication nutraceuticals play major role in therapeutic development. But their success depends on maintaining on their quality, purity, safety and efficacy. With the ever changing human lifestyle the antioxidants defense systems are often overloaded resulting in oxidative stress. Moreover, the levels of antioxidants

defense mechanism decrease appreciably with age. These results in development of great many diseases. Hence research over the past several decades have primarily focused on different nutraceuticals. However and individual's susceptibility to any particular disease predominantly depends upon genetic predisposition and lifestyle disorders like smoking and high alcohol consumption. So the response of nutraceuticals can vary from person to person. Nutraceuticals have proven health benefits and their consumption within their acceptable Recommended Dietary Intakes will keep diseases at bay and allow humans to maintain an overall good health.[7] In the Global market Nutraceuticals and functional foods has become a multi-billion dollar industry and within Canada it is estimated that the Canadian nutraceuticals industry has a potential to grow up to 50 billion US dollars. After US, JAPAN nutraceutical industry is the second largest market in the world which has a steady average growth rate 9.6% per anum. [7]

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Role of Vitamin D in depression

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Abstract :

Depression is a group of conditions which can elevate or lower a person's mood easily and can worsen any chronic medical illness more difficult to cope with. Many people in this country are suffering from an inadequate level of vitamin D. In spite of this vitamin D has been reported as key factor of many health diseases and illness and its several benefits have also been proven recently. People with mental health disorder or depression also have an insufficient level of vitamin D. Depression can be treated by adequate vitamin D levels in person to improve their quality of life. Depression is also the cause of disability throughout the world and it's determined as 4th global burden by WHO and affects about 121 billion people (WHO, 2010).

Keywords :- vitamin D, depression, mental health disorder

Introduction

Many relationships have been established between vitamin D and other mental health disorders, schizophrenia and depression. Depression has been treated with antidepressant medication and psychotherapy for long. Antidepressant therapy has been successfully come out in 60%-80% of the patient but in 25% of people the treatment was not fruitful. Person with depression has a huge tendency to skip their medicine as they feel that is unnecessary or the medicine is doing harm to their bodies in other ways. Mental health illness is a chronic problem and a person with prior illness history has the relapse chance of 70%-80% in addition people with 85% of adhering to the recommended medication have a higher risk of relapse [1]. A level of less than 20ng/ml vitamin D deficiency is directly related to cardio vascular disease, osteoporosis, cancer and diabetes as recently reported. Over a billion of people in this world are deficits in vitamin D levels. Changes in vitamin D levels were not correlated directly with any mood swings. Vitamin D deficiency is endemic in the worldwide population. The factors include lack of exposure to the sunlight and an inadequate dietary intake. **The National Examination Survey (NHANES Health and Nutritional 2001-2004)** found an overall US prevalence of vitamin D deficiency in adolescents of 61% [1]. Vitamin D supplementation is applied to treat depression in adolescents. Supplementation is effective towards incident of depression or psychosis or any other mental health disorder and their recurrence.

Vitamin D is important for CNS both healthy and psychiatric population. Vitamin D receptors are present throughout the brain and associated with negative CNS effects in animal studies when the level is low or deficit.[2]

Vitamin D receptors and its active enzymes are only get stimulated in the hypothalamus, US and substantia nigra and involved in glucocorticoid signaling in hippocampal cells. A depletion in vitamin D shows increased anxiety, decreased activities and muscular and motor impairments and depression too. Vitamin D acts as neuroprotections to hippocampal cells by regulating Ca ion channels. It is also correlated with premenstrual mood symptoms in women. [3] Now a days most countries are faced with a major challenge of suffering with mood disorders. Study on vitamin D levels have been conducted to determine the relationship between severe mental illness with this vitamin and thus this sunshine vitamin does really helps to protect against this disorder or not. The objectives of this study are- to know the health benefits in human body, to increase awareness by this study and also to know the medical value of vitamin D on mental health.

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Assessment and groups at risk for low vitamin

A								
	CALCIUM				VITAMIN D			
	INDIA-ICMR-NIN		USA-IOM		INDIA-ICMR-NIN		USA-IOM	
	2010-RDA	1975-2008	2011-RDA	1997 – AI	2010-RDA	1975-97	2011-RDA	1997 – AI
	mg/day	mg/day	mg/day	mg/day	IU/DAY	IU/DAY	IU/DAY	IU/DAY
INFANTS 0-6 MONTHS	500	500		210	400	400		200
INFANTS 6-12 MONTHS	500	500		270	400	400		200
1-9 YEARS	600	400	700-1000	500-800	400	400	600	200
10-17 YEARS	800	600	1300	1300	400	400	600	200
18-50	600	400	1000	1000	400	400	600	200
51-70	600	400	1200	1200	400	400	600	400
>70 YEARS	600	400	1200	1200	400	400	800	600
PREGNANT & LACTATING	1200	1000	1000-1300	1000-1300	400	400	600	200

B				
VITAMIN D STATUS (ng/ml)	POPULATION BASED VALUES	HEALTH BASED REFERENCE VALUES		
		IOM	ENDO SOCIETY	EUROPEAN CALCIFIED TISSUE SOCIETY
SUFFICIENT	9-37.6	>20	>30	20-30
INSUFFICIENCY	-	12-20 can be adequate or inadequate	20-30	10 to20(Deficient)
DEFICIENCY	<9	<20	<20	<10/12.5(Severe)

Figure 1: RDA of Calcium & vitamin D ICMR, 2020

Data from UK National Diet AND Nutrition Survey indicate that around 1 in 5 adults and 1 in 6 children may have profound vitamin D deficiency. [4] Vitamin D deficiency has some particular signs and symptoms which may vary according to the age and severity. Vitamin D deficiency rickets may appear in case of children. Symptoms of rickets includes bone pain, delayed eruption of tooth and poor growth [5].deficiency of vitamin D in adults can occur muscle weakness, bone pain, difficulty in walking and frequent falls[6]

Some inflammatory bowel disease, celiac disease, and chronic diarrhea [7,8] may appear in persons at more risk. Older adults are often suffers from high risk of vitamin D inadequacy due to low subcutaneous production and intestinal absorption. [9] Many population groups face inadequacy of vitamin D level due to very less exposure to the sun, because of homebound or may be for the clothing choice they make that covers most of the body parts. [10] It has been found in the National and Nutrition Examination Survey (NHANES-III, 1998-1994), MORE THAN 15,000 adults both male and female participants have significantly lower level of vitamin D synthesis compared to people with lighter pigmentation. The American academy of pediatrics recommends that infants who are solely or partially breast-fed get 400 IU/day of vitamin D in first few days till they consume adequate amounts of another vitamin D fortified formula or whole milk. [11, 12] It has been found that in healthy adolescents dietary habits inversely related to vitamin D deficiency. They may be prone to vitamin D deficiency because of obesity.

Impact of sun exposure on vitamin D status

Even a very sunny weather there can be increased prevalence of vitamin D deficiency. This inadequacy can cause skin cancer and a need for sunscreen to protect against this disease. This preventive efforts can reduce our vitamin D levels in our body. UV-B rays can be protected by sunscreen and SPF 30 can decreases vitamin D synthesis by our skin more than 95%. On top of this people now days prefer to spend more time indoors. One person cannot meet his vitamin D needs. Study has been found that it took Caucasians 30% of sun exposure to meet optimal vitamin D level. A short regular exposure to the sun is effective to synthesize vitamin D in our body.

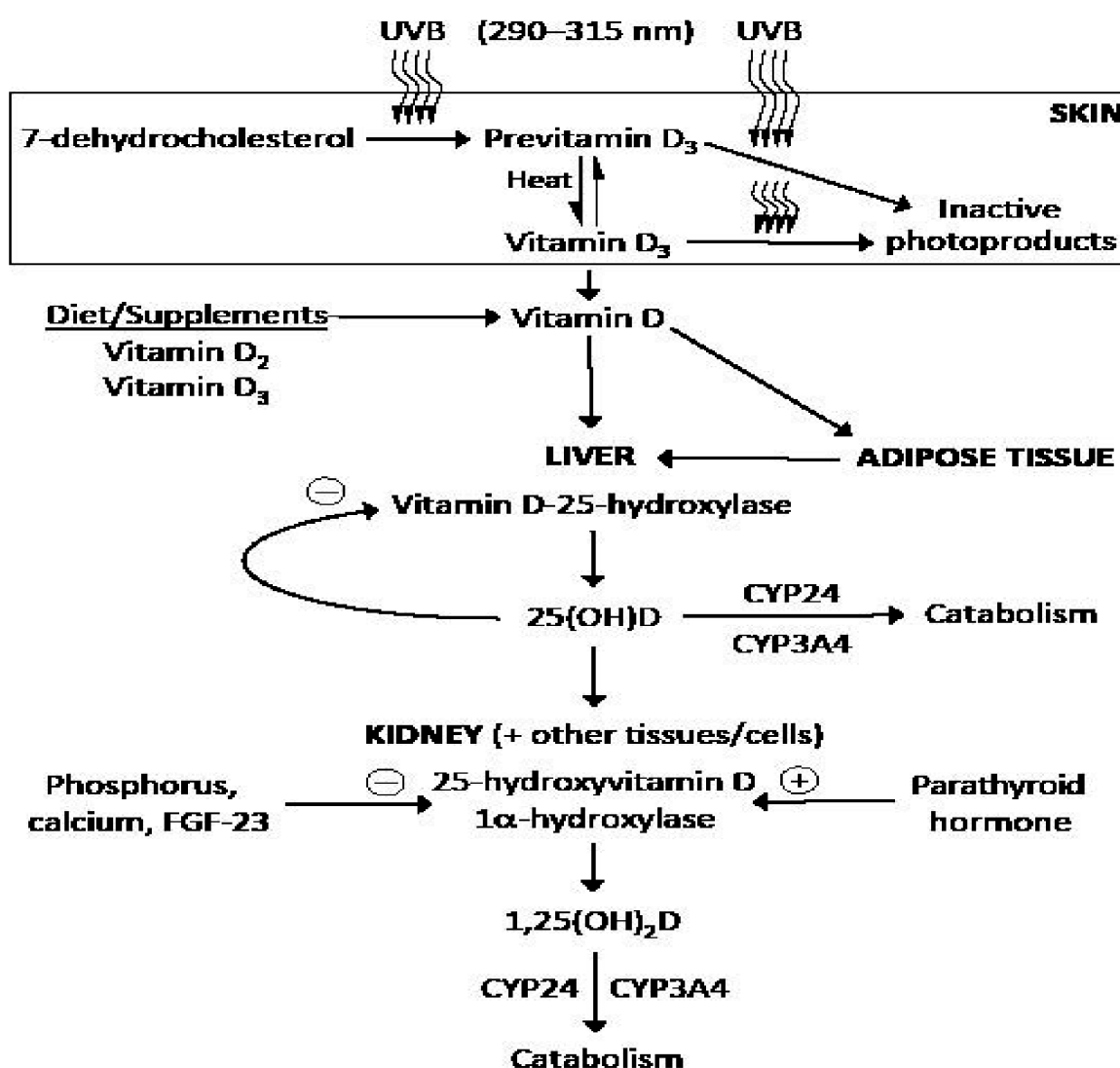


Fig 2 : Synthesis and metabolism of vitamin D

Impact of other factors on vitamin D level

Every individual obtain their vitamin D either exogenously through their dietary sources or by endogenously by activation of vitamin d precursor by ultra violet rays. [13] Dietary sources can be of naturally occurring vitamin D from food, vitamin D fortified food or vitamin D supplementation. As vitamin D is a fat soluble vitamin so the metabolism requires normal digestion and absorption of fat. Vitamin D status can be interrupted by many factors, includes naturally rich food in this nutrients. [14-16]

Association between vitamin D and depression and other mood disorders

Many research have been conducted to find out the relationship of vitamin D to seasonal effective disorder (SAD), schizophrenia and depression. Studies on light therapy have examined to find out that it can improve mood. Partonen, Vakkuri, Lamberg- Allardt and Lonqvist (1996) randomly selected 29 patients among them 16 with SAD and 13 controls to either one hour or 15 minutes of light therapy in the winter morning for two weeks. It has been found that one hour therapy significantly decreased the symptoms of depression in the people with SAD than control groups ($p=.003$). Later Gloth, Alam and Holis (1999) randomly selected 15 participants with

SAD and gave them a dose of 100,000 IU of vitamin D (n=8) or phototherapy (n=7). They reported decreased level of depression in SAD people with one time dose than that of one time phototherapy with no such side effects from the vitamin D dose, the only limitation was that the study was based on only one time dose of vitamin D.

A cross sectional study was made on 80 older people with 40 mild Alzheimer 40 nondemented, aged 60-92 where vitamin D level were assessed and found that 58% of their vitamin D levels were abnormally low. In addition they have presence of active mood disorders [18] But it is not clear whether vitamin D associated with mental disorders or not. There are vitamin D receptors in hypothalamus that is important for neuroendocrine functioning. [19] Vitamin D is also important for brain development [20]. More research are needed to identify long term consequences of vitamin D depletion on brain.

How vitamin D supplementation helps in mental and physical well-being?

A recent study was made of vitamin D supplementation on symptoms of depression in overweight and obese person [21, 22] the participants were randomly selected and then divided into three groups. They were given 20,000 IU cholecalciferol twice per week, once per week, and not at all during this trial for long one year. They all fed Ca supplement of 500 mg daily. The result shown that the 2 groups that received vitamin D have significantly improved their mood (Using the Beck Depression Inventory). Limitation have only overweight and obese included in this study.

This research determines that vitamin D may have the ability to improve many health outcomes. However the vitamin D deficiency can be corrected by dietary sources. Most adolescents who have the tendency to skip their breakfast or lactose intolerance have an inadequate consumption of food to maintain optimal level of vitamin D. They need to take supplements along with their daily diet, in that case vitamin D toxicity with supplements has been largely unsupported. [23, 24]

The study of association between vitamin D and mental health shows that all the studies were made cross – sectional and the adults were selected randomly by their mental health condition, vitamin D levels and according to the presence of SAD, psychosis and other mood related disorders. [25] The studies were also made on the basis of animal and preclinical studies by providing the clue that how vitamin D can lower the risk of depression and mental health.

Sunlight exposure and dietary intake as a source of vitamin D is influence by race. It has been determined that Caucasian population needs to get at least 30% of sun exposure to get optimal level of vitamin D in their body other than that of dietary intake or supplementation [26, 27].

Conclusion

In this discussed paper the group at the risk of low vitamin D deficiency including elderly, adolescents, and obese individuals have been diagnosed with a risk for depression. [28] .This still is an important area of further research that vitamin D has any significant role in prevention and treatment of depression. And if it is really significant that in taking supplements, vitamin D rich diet or spending time in sunlight can do any good to depression patients it would be a very good cost effective solution for the people out there who are battling with severe mental health disorders and depression.

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An analysis of Pharmaceutical market : India Vs World

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Abstract :

The first pharmaceutical company of India was established in the year 1901. For the next 121 years, it has registered impressive growth. Today in terms of volume it is 3rd largest in the world. However, the annual turnover of the Indian market is projected to reach a value of 65 billion USD. This value when contrasted against the global turnover (\$405.52 billion) does not look impressive. This article analyses the various causes of this discrepancy between value and volume of Indian pharmaceutical market.

Keyword : biopharmaceuticals, pharmaceutical market, evolution, annual turnover, global market, comparison, blockbuster drug.

Introduction

The pharmaceuticals sector of the healthcare industry has a huge global market that has expanded significantly over the past few decades. Drug development, manufacture, and marketing have traditionally been at the forefront of the pharmaceutical industry. Since its inception in the nineteenth century, the pharmaceutical industry has come a long way till today. This has become possible due to the introduction of biotechnology-based diagnosis and therapy during the past few decades.

Presently, the global pharmaceutical market encompasses nanotechnology, and artificial intelligence too [1]. This section being a powerful revenue generator has hiked the annual turnovers of the western pharmaceutical companies to a new level. Compared to that, Indian pharmaceutical sector could not keep pace to this growth rate (turnover wise). This article compares the various parameters of Indian pharmaceutical manufacturing companies (organised) in contrast to their global counterparts.

Evolution of Indian pharmaceutical sector

In 1901, Acharya Prafulla Chandra Roy established Bengal Chemical and Pharmaceutical Ltd (BCPL), the first Indian Pharmaceutical Company in Kolkata. BCPL started its journey with the production of simple medicine extracts derived from plant and animal tissues [2]. Next to come in existence, Alembic Chemical Works (1907) & Bengal Immunity (1919) [3,4]. These companies mainly made medicines to treat infectious diseases (malaria, tuberculosis etc.) which was prevalent in India then. Over the next few decades, various small & large-scale industries were established (Indo Pharma, Unichem, Chem Pharma, CIPLA, Zandu Pharmaceutical Works, Calcutta chemicals), but the focus was supplying the local need.

After independence many more companies were established and backed by the foreign investments the pharmaceutical sector grew at a rapid pace. In 1952, the market shares of Foreign MNC (multinational corporation) and domestic companies were 38% & 62%, respectively. In 1970, when patent laws were enforced, the share of the foreign MNC grew up to 68%. The market shares of these MNCs declined continuously thereafter [5].

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The present scenario

The global pharmaceuticals market has grown from \$1454.66 billion in 2021 to \$1587.05 billion in 2022 at a compound annual growth rate of 9.1%. The market is expected to reach \$2135.18 billion in 2026 at a CAGR of 7.7% [6]. Certain countries especially USA, European Union, China and Japan where innovation and development has a fast pace contributes to this exemplary growth rate [7].

Unfortunately, India is not in this league. Although India has almost one-fifth of the world population, its pharmaceutical sector is only 14th largest in terms of annual turnover. However, in terms of volume it is the 3rd largest in the world. In 2021, India's domestic pharmaceutical market increased at 17.7%, up from 13.7% in July 2020. India is expected to reach a market size of USD 65 Billion by 2024 as compared to USD 42 Billion right now [8]. However, this comparison is only valid for the pharmaceuticals of the organised sector. Apart from this, India has got a number of medical systems like ayurvedic, unani, homeopathy, siddha etc. where medicines are produced and consumed by individuals and lacks a systematic record keeping.

Factors affecting the growth of the Indian pharmaceutical industry

The reason for discrepancy between the value and volume of Indian pharmaceutical sector can be easily understood lies in India's economic status. India's public health expenditure is amongst the lowest in the world. It is around 1.02% of its gross domestic product (GDP), a figure which remained almost unchanged in nine years since 2009, lower than most low-income countries which spend 1.4 percent of their GDP on healthcare [9].

India continues to be amongst the worst performers globally when it comes to public spending on health with the latest national health profile revealing that per capita per year government spending on health is a mere Rs. 1,657 [10].

In terms of turnover, Indian turnover is approximately 5% of that of the world. The reason becomes even clearer, if we analyse the profile of the top 10 companies of India and the world [11].

Table 1 : Compares the sale turnover of the leading pharmaceutical companies of India to that of their world counterparts.

World leaders	Sales revenue (US \$)	The flagship product	Indian leaders	Sales Revenue (US \$)	The flagship product
Pfizer	81.2 billion	Becosule (multivitamin) [12]	Sun pharmaceutical Ltd	5.2 billion	Rosuvastatin [13]
Novartis	51.6 billion	Diovan (Valsartan)[12]	Aurobindo pharmaceuticals ltd	3.1 billion	Epzicom(Abacavir and Lamivudin) [14]
Merck	57.6 billion	Keytruda (Pembrolizumab) [12]	Lupin ltd	2.0 billion	Intacept 50 (Etanercept soln.) [15]
Johnson & Johnson	95.58 billion	Tylenol(Acetaminophen) [12]	Cipla	2.9 billion	Ciclopirox olamine [16]
Sanofi	46.3 billion	Amaryl (Glimepiride) [12]	Dr. Reddy laboratories	2.3 billion	Revlimid (Linaliomide) [17]
Roche	63.85 billion	Somnid (Zolpidem) [12]	Cadila	2 billion	Deriphyllin od (Etophylline and Theophylline) [18]
GSK	43.78 billion	Advir (Fluticasone /	Glenmark Salmeterol) [12]	1.25 billion	Fabiflu (Flabipiravir) [19]

Abbvie	56.2 billion	Humira (Adalimumab) [12]	Torrent	1.9 billion	Adfarar (Adalimumab) [20]
Bristol-Myers Squibb	46.4 billion	Revlimid (Lenalidomide)[12]	Alkem	1.3 billion	Clavam (Amoxicillin and clavulanic acid) [21]
			Divi's pharmaceutical	1.2 billion	Naproxen sodium [22]

If we compare the top most pharmaceutical companies of USA and Europe, we could see that innovation is the driving force that dominates the growth of pharmaceutical production. In 2020 Covid came as a pandemic and the top most pharmaceutical company Pfizer developed a vaccine that led them to the top of their turnover chart.

From Table 1, we see one of the top selling products of Novartis is Lucentis which is used for the treatment of macular degeneration. The active ingredient of Lucentis is Ranibizumab, a monoclonal antibody having molecular weight of 48379.97 g/mol. This mega molecule can only be delivered through a novel delivery system and the cost of treatment for one eye is \$56386 [23].

When we contrast the top selling products of the world leaders against their Indian counterparts, the former has a strong inclination towards the development of biological drugs which is rather costly.

In contrast, the top selling products of the Indian pharmaceutical companies mainly have conventional dosage forms. The research of Indian companies is limited to formulation development rather than new molecules. So naturally the Western companies enjoy a monopoly in the field of mega molecular drugs which need the use of sophisticated technologies. This gives them enormous flexibility for profit booking.

Unlike the west, India has a mixed economy, where governmental intervention regarding the cost is a prime issue. This is also a factor affecting their decision regarding price fixation, which in turn affects their research investments. A close study of the Table 1 shows a major revenue earner for pharmaceutical leaders is biopharmaceutical drugs.

Biopharmaceuticals

The term “Biopharmaceuticals” was first coined in the 1980s, which indicates pharmaceuticals produced through biotechnological processes using molecular biology methods. Thus, this group of products are different from the conventional drugs. The biopharmaceutical market has come into being in 1982 when the first biopharmaceutical product, recombinant human insulin, was launched. It represents the fastest-growing segment in International Pharmaceutical market.

Globally, biopharmaceutical generates 20% revenue of the pharmaceutical companies. The efficacy and safety of biopharmaceutical products, combined with their ability to address previously untreatable conditions has created a strong demand and significant profit. Many of the biopharmaceuticals have reached standards for blockbuster drugs (sales value more than \$1 billion). The top 15 biopharma products each enjoy annual revenue of more than \$2 billion. Humira used in rheumatoid arthritis and other inflammatory diseases, generated a sale of more than \$10 billion in 2014\$20 billion in 2019 and \$16 billion in 2020 [24].

Biopharmaceutical drugs are also used for the treatment of the board spectrum of diseases including cancer and metabolic disorders.

They are usually administered through targeted delivery systems to the target sites that ensure high specificity and activity [25,26]. Since the registration of adalimumab (brand name Humira) in 1986, the first monoclonal antibody, its sale has grown every year. As a result of the government's rising budgetary allocation for the sector, India's strength in biotechnology R&D has increased. The thrust areas of research include bioprocess engineering, gene manipulation of microbes and animal cells, downstream processing, stem cell biology, bioinformatics,

proteomics, genomics etc. [27]. Finally, armed with the recombinant protein technology and gene therapies, the Indian biopharmaceutical industry is gearing itself to enter into the developed market [28].

Gene therapy

In gene therapy, genes are used as a therapeutic target. It aims to cure the diseases through manipulation of the causative genes. These therapies include deciphering the genetics and correcting the abnormalities through bioengineering extrachromosomal materials are deliver to target cells through manipulating vectors [29]. The United States was the first country to start gene therapy clinical trials worldwide. Major pharmaceutical companies which are interested in gene therapy Gilead Sciences, Bristol-Myers Squibb, Novartis AG, Amgen, Merck, Organogenesis Holdings, Dendreon, Vericel, Bluebird Bio and Fibrocell Science [30]. India is not much behind in this race. Today India have been established a total of 10 gene therapy research laboratories [31]. Currently, gene therapy is attempted only in in laboratories; its application is still experimental. However, once it gets recognition of an established medicine it will become a major revenue earner for the pharmaceutical companies. These projects a major improvement in the status of the Indian pharmaceutical sector.

Conclusion:

India hosts a population of one fifth of the world but its pharmaceutical sector ranks a lowly fourteenth in terms of sales value. Low overhead income and governmental intervention are mainly responsible for this but recently there has been remarkable advances in the field of biotechnological research and gene therapy which is likely to boost the growth of Indian pharmaceutical sector to a great extent.

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