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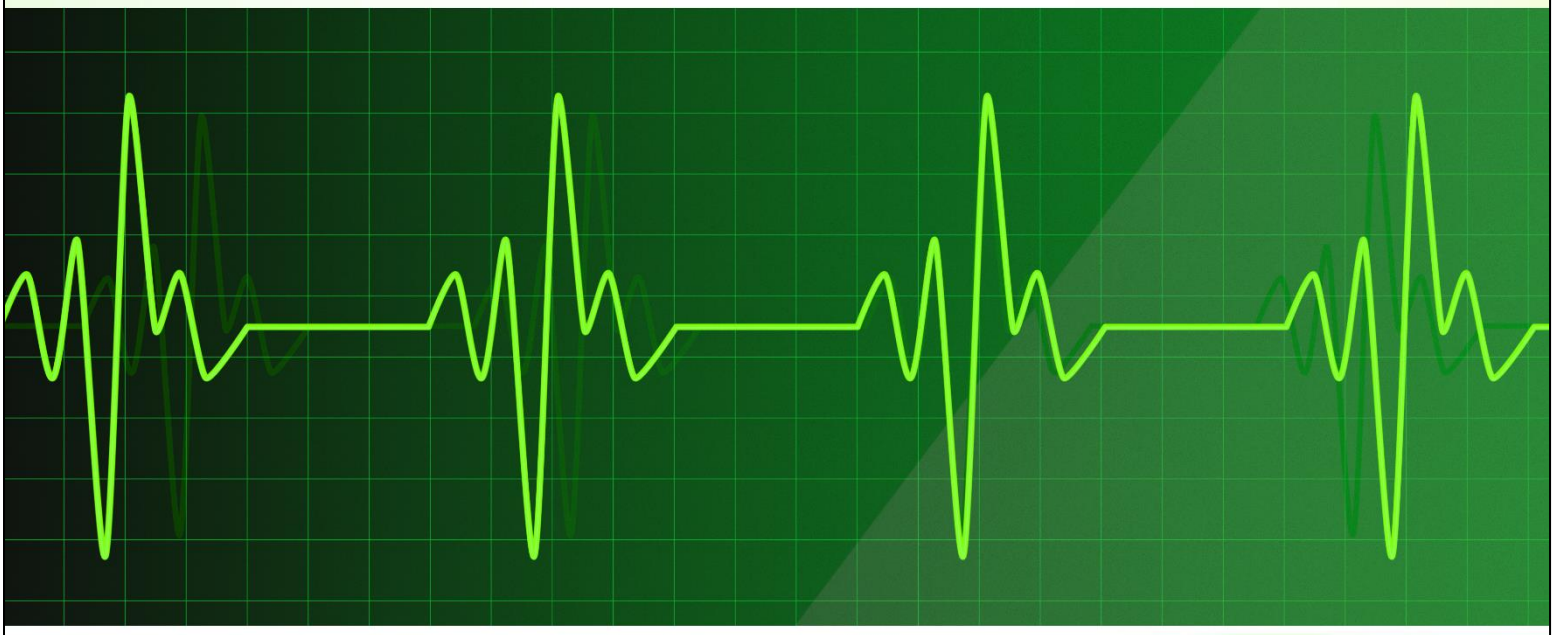
Advances in Biomedical and Healthcare Science

Volume I



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PREFACE

*We are delighted to publish our book entitled "**Advances in Biomedical and Healthcare Science Volume I".** This book is the compilation of esteemed articles of acknowledged experts in the various fields of medicines, health science, pharamaceutical science and life science providing a sufficient depth of the subject to satisfy the need of a level which will be comprehensive and interesting. It is an assemblage of variety of information about rapid advances and developments in various subjects. With its application oriented and interdisciplinary approach, we hope that the students, teachers, researchers, scientists and policy makers in India and abroad will find this book much more useful.*

The articles in the book have been contributed by eminent scientists, academicians. Our special thanks and appreciation goes to experts and research workers whose contributions have enriched this book. We thank our publisher Bhumi Publishing, India for taking pains in bringing out the book.

Finally, we will always remain a debtor to all our well-wishers for their blessings, without which this book would not have come into existence.

- Editors

CONTENT

FORMULATION OF SUGARLESS MEDICATED LOGENGES FOR DIABETIC PATIENTS

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Abstract:

The main objective of the present study is to develop sugar free medicated lozenges for diabetic patient to treat the dryness of mouth and control glucose level by the using different herbal drugs. Mouth dryness is very common symptoms in diabetes. Dry mouth, or xerostomia, caused when a person's salivary glands do not produce sufficient saliva to keep the mouth moist. Mouth dryness can be a symptom of diabetes and also a side effect of the medication that treats diabetes. Mouth dryness is the most common problems that people living with diabetes experience. The formulations of medicated lozenges contain xylitol natural sweetener and different therapeutically active compound like Gymnamic acid, cinnamon oil, liqorice Giloy extract which are effective in control dryness of mouth as well as control the glucose level in diabetic patients. This formulation contain flavoring agent such as menthol, acacia and guar gum as a gum base. Preservative are used for prevent unconditional growth of bacteria. Sugar free lozenges have bright future as a novel method of delivering drugs for local action and systemic effect.

Keywords: Sugarless, Xerostomia, Diabetes, Lozenges

Introduction:

Lozenges are flavored medicated dosage form intended to be sucked and held in mouth or pharynx. These drug deliveries provide ease of administration for patients. The drug delivery used for a large dose administration of drug in the form of lozenges. Lozenges are solid preparations that consist one or more medicaments, usually in a flavored, sweetened base, that are intended to dissolve or disintegrate slowly in the oral cavity. Lozenges can be prepared by molding or by compression of sugar-based tablets (1). Molded lozenges are sometimes called as pastilles, whereas compressed lozenges may be referred to as troches. Generally lozenges are used for patients who cannot swallow solid oral dosage forms well as for medications designed to be released slowly to yield a constant level of drug in the oral cavity. Lozenges historically have been used for the relief of minor sore throat pain and irritation and have been used extensively to deliver topical anesthetics and antibacterial drug. Patient compliance is increase

with buccal drug delivery due to the accessibility of the cheek and lack of invasive measures (2). This investigation deals with formulation of medicated sugar free lozenges containing the herbal extract.

Diabetes mellitus is a chronic disorder. DM is a group of metabolic Disorders in which there is increase blood sugar level in blood. Diabetes is due to either the beta cells of pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. In the diabetic patients mouth dryness is very common symptoms. Dry mouth, or xerostomia, occurs when patient's salivary glands do not produce enough saliva to keep the mouth moist. Mouth dryness can be a symptom of diabetes and also a side effect of the medication that treats diabetes. Mouth dryness is the most common problems that people living with diabetes experience.

Advantages

- It has a pleasant taste and will extend the time a quantity of drug remains in the oral cavity to elicit local activity.
- Systemic absorption of drugs can be possible through buccal cavity.
- It can be prepared with minimal equipment.
- Taste of the drugs can be masked by natural sweeteners and flavors used in the formulation
- Formulated lozenges shows multiple benefits in diabetic patient such as-
- Increase saliva secretion in oral cavity.
- Licorice and menthol nourish the mucous membrane and promote saliva secretions.
- Provide systemic and local effect
- Activate salivary gland to produce saliva
- To control glucose level in diabetic patients
- Due to use of herbal drugs it's minimize side effect
- Cost effective dosage form

Material and Methods:

Materials

Types of Lozenges

1. Hard candy Lozenges
2. Soft Lozenges
3. Chewable Lozenges

Material used in formulation of sugar free medicated lozenges

Table 1: The active ingredients used for production of hard candies lozenges

Sr. No.	Herbal Drug	Biological Name	Family	Chemical Constituents	Uses
1.	**Gymnema**	*Gymnema sylvestre*	Apocynaceae	Gymnemic acids	Anti- Dibetic
2.	**Cinnamon**	*Cinnamomum* zeylanicum	Lauraceae	Cinnamaldehyde, Cinnamic acid	Anti- Dibeticantibacterial, antifungal, antiseptic, carminative, stomachic
3.	**Liquorice**	*Glycyrrhiza glabra*	Fabaceae	Glycyrrhizinic acid	mouth sores,
4.	**Menthol**	*Mentha piperita*	Labiatae	limonene, Terpenoids	ointments, cough drops, and nasal inhalers

Figure 1: Herbal Drug used in formulation

1. Active Ingredients

A. Gymmnemic acid

Gymnema sylvestre, Family: Asclepiadaceae, generally known as "gurmar or madhunashini" for its different property as sugar cutter, is a important herb in the Ayurvedic system of medicine. The chemical constituents responsible for sweet suppression activity includes triterpene saponins called as gymnemic acids, gymnemasaponins, and a polypeptide, gurmarin. *Gymnema sylvestre* exhibits a wide range of therapeutic activities as an effective on diabetes, besides being used for arthritis, diuretic, anemia, osteoporosis, hypercholesterolemia, cardiopathy, asthma, constipation, microbial infections, indigestion, and anti-inflammatory. *G. sylvestre* has superior treatment of diabetes as it shows positive effects on blood sugar homeostasis, controls sugar cravings, and promotes regeneration of pancreas to produce insulin.

B. Cinnamon oil

Cinnamon oil contains essential compounds that may promote heart health and diabetes treatment. It shows antioxidant properties may help prevent cancer disease and combat skin inflammation. Cinnamon oil is derived from the bark or leaves of several types of cinnamon trees, including the *Cinnamomum verum* tree and the *Cinnamomum cassia* tree.In both

human and animal models, cinnamon has been shows to have positive effects on insulin release from pancreas, which means it can help keep blood sugar control and therefore prevent chronic fatigue, moodiness, sugar cravings and overeating.

C. Licorice

Glycyrrhizin is a saponin-like compound that responsible for the main sweet flavor for Glycyrrhiza glabra (licorice), which is also act as immunomodulating, anti-inflammatory, hepato- and neuro-protective, and antineoplastic activities. Glycyrrhizin modulates certain enzymes responsible in inflammation and oxidative stress, and downregulates certain pro-inflammatory mediators, thereby protecting against inflammation- and reactive oxygen species (ROS)-induced damage. Glycerrhizin may also prevent the growth of susceptible tumor cells.

2. Natural sweetner

Xylitol

Xylitol is relatively sweet and has an advantage in lozenge formulation with respect to its lack of caries production.

3. Gum Acacia & guar gum

Gum Acacia (GA) is a natural branched-chain multifunctional hydrocolloid with a highly neutral or slightly acidic, arabino-galactan-protein complex consist calcium, magnesium, and potassium. Gum Acacia is dried exudate obtained from the stem and branches of Acacia trees manly *Acacia senegal* and *Acacia seyal*.

Guar gum is one of the wonderful representatives of that new generation of plant gums. Its source is an annual pod-bearing, droughtresistant plant, called Guar, or cluster bean (Cyamopsis tetragonolobus or C. psoraloides), belonging to the family Leguminosae.

4. Flavoring agent

Menthol

Menthol is a covalent organic compound made synthetically or obtained from peppermint or other mint oil or mint plant. Produce clear or white waxy, crystalline substance, menthol is usually solid at room temperature. Menthol produce anesthetic properties and anti-irritating properties locally, thus it is commonly used to relieve minor throat irritations by the providing cooling effect.

5. Colorant

Dyes and other organic coloring agent may degrade by heat or light via oxidation, hydrolysis, photo oxidation, and etc. The compatibility with drug, excipient, and process conditions should be studied before selection of colorant. Colorant may increase elegance property of dosage form.

Preservative

In the solid dosage form usually there is no need to incorporate preservatives. But the hard candy lozenges are hygroscopic in nature, the water content may increase and bacterial development may occur if they are not packaged properly. Methylparaben, propylparaben and butyl paraben is used as a preservative in mostly used in various dosage forms.

Preparation of sugarfree hard candy lozenges

Open fire cooking was also conducted to prepare sucrose-free hard lozenges.The samples were formulated according to the mixture design (Table 2) with the following ingredients: Firstly Acacia, guar gum dissolve in water with heat. In another beaker Xylitol, gymnnemic acid, cinnamon oil, giloy extract, & menthol; Dissolved in water were heated until a temperature of 170 ˚C was reached, and the mixture was then cooled after that in which add preservative and glycerol. At 112–115 ˚C, the mass was blended with *gymnnemic acid*, cinnamon oil, giloy extract, and menthol. Afterward, The final mixture was poured into silicone molds and cooled down at 20 ˚C for 5 min. Solid lozenges removed from the molds were packed in aluminum bags and stored in a refrigerator (10 ˚C) until required for analysis(3).

Table.2: Formulation Table

Sr. No.	Ingredients	Quantity Taken
1.	Gymnemic acid	0.5 gm
2.	Cinnamon Oil	3-4 drops
3.	Giloy extract	0.5 gm
4.	Menthol	3-4 drops
5.	Xylitol (60%)	6.7 gm
6.	Xylitol Powder	30.7 gm
7.	Acacia	2 gm
8.	Guar Gum	2 gm
9.	Glycerol	70 ml
10.	Methyl Paraben	0.4 gm
11.	Propyl Paraben	0.2 gm
12.	Water	Q.S

Pre-formulation studies

Identification of herbal extract and other excipients used in the formulations

Herbal extract was identified by organoleptic evaluation as per specifications laid down in respective monographs given in I.P. 2010 for each sample before using them in the

formulations. Since intended formulations were supposed to be sucrose-free; hence, all raw materials used were tested for freedom from traces of sucrose using qualitative and quantitative tests for presence of sucrose. The raw materials which conformed to 'absence of sucrose' were used in the lozenges preparation.

Drug-excipient compatibility studies

The compatibility studies provide the basis for the selection of excipient for the particular drug in the fabrication of the dosage form. The study was carried out to establish that the therapeutically active drug did not undergo any changes after it was subjected to processing steps along with excipient during formulation of lozenges. The drug and excipient were checked for their compatibility by Fourier Transform Infrared Spectroscopy. The I.R. spectral peaks of pure drug and drug excipient in potassium bromide (KBr) pellets were evaluated using FTIR Spectrophotometer (Bruker series) (4). The drug and excipient compatibility studies were performed by preparing physical mixture of drug and excipient in different ratios (1:1, 1:1, 1:5, 1:10, 1:10) subjecting samples at 50°C for three weeks. At the end of three weeks, the characteristic changes if any were recorded and FTIR spectra of all the samples were taken.

Evaluation of Sugar Free lozenges

Physical Characteristics of molded Sugar free Lozenges

General appearance, diameter and thickness of sugar free lozenges were recorded. The appearance of all lozenges, its visual identity and overall elegance is essential for patient acceptance. The formulated sugerfree lozenges were evaluated for size, shape, organoleptic characters such as colour, odour and taste. The diameter and thickness of the lozenges were recorded using Micrometre instrument. For the evaluation of diameter and thickness twenty lozenges were taken from each batch and average thickness and diameter was mesaured.

Weight variation / uniformity of weight

For the determination of weight variation twenty lozenges of each formulation were selected at random and weighed individually and collectively on a digital weighing balance. The weight of individual lozenge was recorded. For the calculation of weight variation and the individual weights were compared with the average weight (5). The weight of not more than two lozenges must not deviate from the average weight by more than 5 %.

Hardness

Hardness of lozenges was evaluating using Monsanto Hardness tester by taking six lozenges from each formulation. The unit expressed in Kg / cm^2.

Friability

For the evaluation of friability twenty lozenges was measured using a Roche Fribilator. Twenty pre-weighed sugar free lozenges were rotated at 25 rpm for 4 minutes. The lozenges

were taken out and de-dusted and were reweighed and the percentage of weight loss was calculated. Friability of lozenges was found to be less than 1% in the range of 0.21% to 0.98%.

Percentage friability = [(Initial Weight – Final Weight) /Initial Weight] x 100

Wetting time and water absorption ratio

For the determination of wetting time ad water absorption ratio, A piece of tissue paper folded twice was kept in a Petri plate (internal diameter 5.5 cm) containing 6 ml of purified water. A lozenge contains a small amount of Rosaline dye powder on the upper surface was placed on the tissue paper. The time required to develop a red colour on the upper surface of the lozenge was recorded as the wetting time (6). The same procedure used without Rosaline dye powder was followed for determining the water absorption ratio R which was determined according to the following equation.

$$RR = [(Wa - Wb)/Wb] \times 100$$

Where, W_b and W_a were the weights of the lozenges before and after use.

Disintegration time

Disintegration time of sugar free lozenges was measured in artificial saliva (pH 5.8) according to the USP 24 method at 37 ± 0.5^0C. The disintegration time of 6 individual lozenges were recorded.

Drug content and content uniformity

Drug content in lozenges formulations was determined by U.V. Spectrophotometric method. The content uniformity was determined in each of twenty lozenges spectrophotometrically.

Moisture content / Water content

Moisture content / Water content were estimated by using Karl Fisher apparatus.

***In-vitro* dissolution studies**

The drug release from lozenges was estimated using USP dissolution testing apparatus type 2 (paddle method). The In-vitro dissolution test was determined by the using of 900 ml of artificial saliva, pH 5.8 at 37 ± 0.50C and 50 rpm. The 10 ml sample was withdrawn from the dissolution apparatus at different time intervals and the samples were replaced with fresh dissolution medium (7). The samples were filtered through a 0.45 µ membrane filter and diluted to suitable concentration with artificial saliva, pH 5.8. Absorbance of this sample was measured at 225 nm by the using of Shimadzu UV/Vis double-beam spectrophotometer. The cumulative percentage drug release was calculated using an equation obtained from a standard calibration curve (8).

Stability data

The optimized formulation F6 was subjected to stability studies, by storing at 40°C ± 2°C / 75% ± 5% RH for a period of 30 days. At the optimized period, sample were evaluated for physical appearance, drug content, disintegration time and *in-vitro* dissolution studies (9).

Results and Discussion:

The medicated lozenges are differs from conventional tablet due to properties of organolepticity, non-disintegrating characteristics and slower dissolution profiles.

The lozenges of final batch F6 showed smooth appearance and no cracks were found while inspecting using magnifying glass (5X and 10X) with very smooth flat surface and light orange yellow color with aromatic fragrance with mild sweet taste for using licorice and cooling effect. Lozenge thickness was almost uniform in all formulations and was found to be in the range of 3.08 mm to 3.05 mm. The hardness of each batch was noted and found to be in satisfactory range of 4.0 to 4.4 kg /cm^2.

Wetting time and water absorption time is used as a marker from the ease of the lozenge disintegration in buccal cavity. It was observed that wetting time of final batch F6 of lozenges was in the range of 15-33 seconds. The lozenge of optimized batch disintegrated in 90 Seconds which is acceptable for mouth dryness Lozenges. Disintegration time of sugar free lozenges was within acceptance criteria of 1 minute to 1.5 minutes.

The drug content of the prepared sugar free lozenges was in the acceptance criteria and the correlation of variation was found to be less than 0.010%, indicating uniformity of the active ingredient in the prepared lozenges. Water content or water absorption was found within range of 1.82% w/w to 1.77% w/w. The Stability Studies evaluation showed that Physical appearance of lozenges remains unchanged. Dissolution profile was more than 95.0% in 30 minutes. Hardness, Thickness, Friability, Average Weight and Water Content of lozenges were within the satisfactory criteria. Disintegration time remained unchanged. From one month stability data, no significant change in parameters was observedindicating no degradation of active ingredient.

Table 3: Parameter of prepared sugar free lozenges

Formulation	Avg weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/ cm2)	Friability (%)
F1	767.41 ± 0.11	3.08 ± 0.0005	15.85 ± 0.13	4.0 ± 0 .13	0.98
F2	713.94 ±0.03	3.22 ± 0.0010	15.03 ± 0.02	4.2 ± 0 .09	0.38
F3	738.94 ± 0.12	3.30 ± 0.0031	14.03 ± 0.02	4.5 ± 0 .15	0.27
F4	699.94 ± 0.23	3.21 ± 0.0031	15.98 ± 0.02	4.3 ± 0 .04	0.21
F5	737.44 ± 0.27	3.10 ± 0.0051	15.21 ± 0.03	4.2 ± 0 .02	0.47
F6	741.04 ± 0.41	3.05 ± 0.0005	14.01 ± 0.02	4.4 ± 0.03	0.21

All the prepared formulations were subjected to physical–chemical evaluations like weight variation, thickness, hardness, friability, drug content, disintegration test and wetting time were carried out in order to evaluate the suitability of the formulation with respect to the dosage form and intended therapeutic use. The average weight of each batch was not maintained

constant, but the weight variation was within ± 5% of variation. The hardness of each formulation was estimated and found to be in acceptable range of 4 to 4.4 kg / cm^2. Lozenges, thickness was almost uniform in all formulations and was found to be in the range of 3.08 mm to 3.05 mm. Friability was found to be less than 1% and considered to be satisfactory in the range of 0.98% to 0.21%.

Table 4: Parameter of prepared sugar free lozenges

Formulation	Disintegration Time (sec)	Water content (W/W)
F1	64±1	1.82±0.09
F2	63±2	1.91±0.07
F3	51±5	1.89±0.03
F4	52±4	1.47±0.10
F5	48±3	1.79±0.09
F6	90±2	1.77±0.04

The prepared sugar free lozenges were evaluated for disintegration time, water content. The results of all the test formulations were within the limit and passed. Disintegration time was within acceptance criteria up to 1.5 minutes. Water content by Karl fisher method was also within the range of 1.82% w/w to 1.77% w/w.

***In-vitro* Dissolution Study**

The results of In-Vitro release profiles of different formulations are summarized in table 5.

Table 5: *In –Vitro* release profiles study of different formulations

Time	Drug Release profile (% drug release)					
	F1	F2	F3	F4	F5	F6
10	81±0.80	82±0.31	81±0.56	82±0.70	82±0.01	87±0.04
15	85±0.34	87±0.65	89±0.04	90±0.63	89±0.48	89±0.79
20	92±0.30	92±0.09	93±0.29	93±0.90	93±0.09	94±0.34
30	96±0.21	94±0.35	98±0.89	97±0.01	96±0.37	99±0.01

In- Vitro drug release profile for all formulations were measured by using artificial saliva (pH 5.8) as dissolution medium for 30 minutes. From the results obtained it was observed that the formulation F6 showed better release rate 99% within 30 minutes than other formulations. Therefore, it was concluded that F6 was desired formulation and was taken for further stability studies.

Stability analysis

The results of stability study of optimized formulation of Sugar Free lozenges at accelerated conditions are summarized in table 6 to10.

Table 6: Physical and chemical parameter of Sugar free Lozenges (F6) after 1 month at 40^0C ±2^0C/75% RH ±5% RH

Parameter	Initial	1 month
Description	Light orange to pale yellow, oval shaped flat lozenges	No change
Average weight (mg)	741.04±0.41	No change
Hardness (kg /cm^2)	4.4	3.98
Thickness (mm)	3.05	No change
Friability (%)	0.21	0.18
Water content (w/w)	1.77	1.54

Packing: Blister pack

Table 7: Dissolution profile of sugar free lozenges (F6) after 1 month at 40± 2^0C / 75% RH± 5% RH

Time (min)	Drug release percentage (%)	
	Initial	Final
10	87±0.04	87±0.98
15	89±0.79	89±0.01
20	94±0.34	93±0.13
30	99±0.01	98±0.81

Packing: Blister pack

Table 8: Physical and chemical parameter of Sugar free Lozenges (F6) after 1 month at 40^0C ±2^0C/75% RH ±5% RH

Parameter	Initial	1 month
Description	Light orange to pale yellow, oval shaped flat lozenges	No change
Average weight (mg)	741.04±0.41	No change
Hardness (kg /cm^2)	4.4	3.98
Thickness (mm)	3.05	No change
Friability (%)	0.21	0.18
Water content (w/w)	1.77	1.54

Packaging- HDPE Bottle

Table 9: Effect of Temperature on hardness of lozenges

Storage temperature	Hardness (kg/cm^2)			
	1st week	4th Week	8th Week	12th Week
RT (28 ±2^{0}C)	4.01	4.04	4.50	4.02
37^{0}C	4.01	4.11	4.60	4.03
45^{0}C	4.02	4.03	4.54	5.06

Table 10: Effect of temperature on disintegration time of lozenges

Storage temperature	Disintegration time (Sec.)			
	1st week	4th Week	8th Week	12th Week
RT (28 ±2^{0}C)	90.2	90.1	90.5	90.3
37^{0}C	90.1	90.1	90.1	90.4
45^{0}C	90.3	90.0	90.2	90.3

Description remains unchanged. Dissolution was more than 95.0% in 30 minutes. Hardness, thickness, friability, average weight and water contents were within the satisfactory range from one month stability data no significant changes in various parameters were observed in stability studies carried under accelerated conditions for optimized formulation F6.

Conclusion:

Based on the optimization of parameters it was felt that molded lozenges of herbal extract can be prepared by molding method using xylitol as sucrose-free base. These lozenges may have wide acceptability among diabetics. All herbal extract was selected as a therapeutic agent for the mouth dryness and hypoglycemic agent in diabetic patients and was found to be of standard grade and all excipient used in the study were found to meet the specifications as per I.P 2010. All the samples showed absence of sucrose. The granules were prepared in manner similar to that used for any compressed tablets. The formulated dosage form is therapeutically effective in dryness of mouth to increase saliva secretion in mouth and moisten the mucous membrane. Hyperglycemia is a major problem in world mostly in younger generation and old people also. The established dosage form is effective in lower glucose level in blood by the absorption through oral mucosal membrane and absorption through stomach after sucked lozenges reach in stomach. These formulation contain various therapeutic ingredients like gymmema extract, cinnamon oil, liqourice extract , Giloy extract and menthol, which shows anti- diabetic properties and promote saliva secretion in mouth.

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PREDICTION OF CRISPR CAS SYSTEMS USING BIOINFORMATICS TOOLS

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Introduction:

Genome editing, also known as insertion, deletion, and replacement of DNA, are the alteration of DNA at a specific target site in a wide range of cell types and organisms. This results in the inactivation of target genes, the acquisition of novel genetic traits, and the correction of pathogenic gene mutations. Genome editing technology has recently emerged as being the most effective way to study gene function, investigate the pathophysiology of genetic disorders, create new gene therapy targets, breed crop varieties, and other topics due to the rapid development of the biological sciences. transcription activator-like effector nucleases (TALENs), Zinc finger nucleases (ZFNs), and the RNA-guided CRISPR-Cas (Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR-associated protein) nucleases systems are the three most common genome editing methods available today. CRISPR-Cas system is developed the most general genome editing tool in molecular biology labs all over the biosphere because of the benefits of their straightforward design, low price, high performance, strong reproducibility, and quick cycle times (Xu & Li, 2020).

The three components of a CRISPR-Cas system are an CRISPR array of repeats divided by distinct sequence known as spacers, a leader sequences upstream of the array that covers the promoter and forms a transcript with the array, and a set of associated cas genes that convert the protein needed for further handing out of data enclosed within the array (Rodolphe Barrangou & John van der Oost, 2013). CrRNA and Cas proteins combine to produce highly specialized RNP complexes called as Cas module-RAMP (Cmr) or Cascade (Nam et al., 2012). The both adaptation and interference processes sometimes need an extra motif near the protospacer, called as the Protospacer Adjacent Motif (PAM) (Shah *et al.*, 2013). Depending upon that effector module structure, CRISPR-Cas systems have already been divided into classes of two broad, at least six kinds, and multiple subtypes. CRISPR-Cas systems of class I use varies-protein effector complexes, whereas CRISPR-Cas systems of class II use single-protein effectors (Makarova *et al.*, 2015). The vast majority of CRISPR-Cas systems are Class I systems found in bacteria and archaea. This network is made up of 6 to 10 Cas proteins that work in huge Cascade or Cmr complexes. Class II networks, on the other hand, are small, with only 2 to 4 Cas protein, and a assumed to be unique to bacteria until a metagenomic investigation identified Cas9 proteins

encoded in archaeal genome. Class II CRISPR-Cas system have permitted effective genome editing in eukaryotes due to their compact design (Burstein *et al.*, 2016). CRISPR-Cas9 entails an extra RNA element, the tracrRNA (trans-activating crRNA), which really is partly corresponding to the crRNAs and functions as an adaptor to bind crRNAs to the RNP complex (Deltcheva *et al.*, 2011). Today, synthetic fusions of crRNAs and tracrRNAs, known as single guide RNAs (sgRNAs), are commonly employed in genome editing applications.

Around 90% of archaeal and 48% a system of adaptive immune that defends them from viruses, phages, and other external genetic elements. It is made up of a group of Cas (CRISPR-associated) genes that encode Cas proteins with endonuclease activity and CRISPR repeat-spacer arrays, which can be additional translated into CRISPR RNA (crRNA) and trans-activating CRISPR RNA (tracrRNA). When foreign genetic elements penetrate prokaryotes, Cas proteins can break the invaders' DNA to brief bits, which are subsequently incorporated into the CRISPR array as new spacers. When the similar attacker outbreaks again, crRNA will detect it right away and pair with the extremal DNA, which directs Cas protein to cleave specific target regions of foreign DNA, defending the host (Xu & Li, 2020).

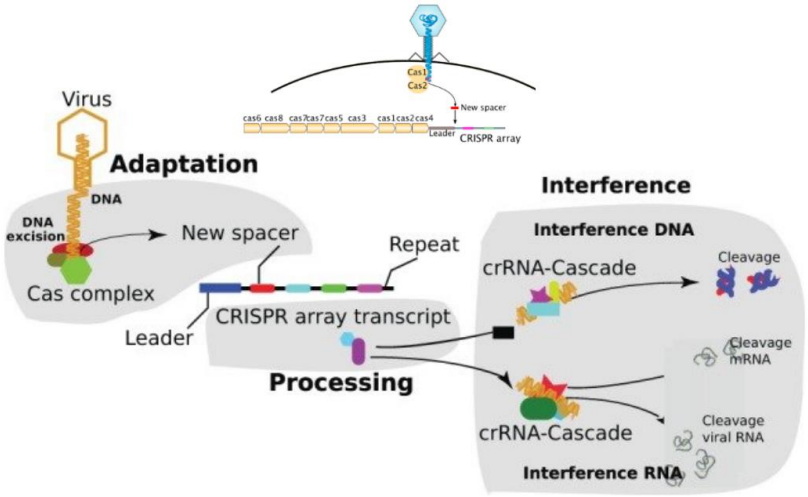

Figure 1: The 3 important phases of CRISPR-Cas immune system. The adaptation/acquisition phase, Cas proteins excise the protospacer sequences from non self DNA and insert it to the repeat, adjacent to the leaders at the CRISPR loci. CRISPR arrays are transcribed and then processed to multiple CRISPR RNA, each carrying a single spacer sequence and part of the adjoining repeat sequence. The interference phase, the CRISPR RNAs are assembled into varies classes of Cascades (protein targeting complexes) that anneal to, and spacer, cleave hit sequences on whichever attacking element or their transcriptions. Cas2 and Cas1 replicate the incorporate and protospacer it obsessed by the CRISPR array close to the region of leader during the acquisition/adaptation stage. (Alkhnbashi *et al.*, 2014, 2020).

Computational research in the area has evolved along both paths, with protein-coding genes analyses on one side and predictions of nucleotide interaction on the further. Many hours and dollars have been spent categorizing CRISPR-Cas systems since their discovery. This categorization procedure resulted in the finding of new cas genes, resulting in continual improvement of annotation and classification techniques (Makarova *et al.,* 2015). The newly found protein and their task in immunity of CRISPR-Cas have the focus of each iteration's biochemical study, which led to the finding of further kinds, such as the recently defined Type IV, VI, and V systems (Vestergaard *et al.,* 2014). The construction of the CRISPR array and the arrangement of cas genes and are currently utilized to categories distinct CRISPR systems. Along with a rising breadth of accessory genes, the amount of known cas gene groups expanded from 27 of 4 (Makarova *et al.,* 2015). Due to this quick expansion, we have only seen the top of the iceberg. Metagenomic data sets have the potential to be a high foundation of cas gene groups & CRISPR-Cas types.

The CRISPR-Cas system was discovered and new functionalities are discovered with the help of bioinformatics. Yoshizumi Ishino published the initial description of the distinctive repeat spacer architecture of arrays (Ishino *et al.,* 1987). Mojica later shown, with the use of bioinformatics analyses, that arrays are found in various bacterial and archaeal genomes in addition to *Escherichia coli* (Mojica *et al.,* 2000). It was determined through further bioinformatics analyses those spacers matched bacteriophages, supporting the correct assumption that CRISPR-Cas systems role as a system of acquired immune (Mojica *et al.,* 2005; Pourcel *et al.,* 2005). Later, a different bioinformatics analysis on spacer matches correctly foreseen that the primary target systems of CRISPR Cas would be DNA rather than RNA (Shah *et al.,* 2009). Therefore, both the finding of CRISPR systems and a creation of the early functional hypotheses relied heavily on bioinformatics.

Many more intriguing elements of CRISPR-Cas systems may be investigated using specialized bioinformatics methods. Among these are the discovery of crRNA target sequences, the prediction of CRISPR leader sequences, the characterization of PAM motifs, and so on. Design of CRISPR-Cas9 guides. CRISPR's broad applicability through gene editing, as well as its simple guidelines for manipulative sgRNA, has providing an outstanding opportunity for bioinformatics researchers to gain an understanding of numerous aspects of the CRISPR mechanisms through computational approaches and the expansion of software that classifies potential sgRNA sequences in genomes. Although there are several design tools, databases available, and web servers, not all of them are the same. Respectively has a distinct edge over the other. As a result, in order to make the task simpler for researchers all over the world, it is necessary to have an eye out for numerous CRISPR design software founded on some of the possible benefits, such as functionality, convenience of use, research demands, availability, and,

more particularly. The sections that provide an overview of tools for these and other objectives, as well as recommended practices for effective CRISPR-Cas studies.

CRISPR-Cas systems prediction

In general, CRISPR-Cas system prediction is based on the discovery of CRISPR arrays and cas genes. While standard protein homology search algorithms, like as Pfam/HMMer3 (HMMER is now virtually as fast as BLAST), may identify cas genes, CRISPR arrays are significantly less conserved (spacer acquisition) & hence require new methodologies. The main aim behind all of the approaches provided here is to find repeating sequences that match particular repetition length, spacing, similarity, or number requirements.

1. CRISPR Finder & CRISPR CasFinder

Based on (Grissa *et al.*, 2007b), CRISPRFinder (Update stop at 2017) and its newest descendent CIRSPRCasFinder (Couvin *et al.,* 2018) are the most known web tools for identification of CRISPR array. They begin their search for repeating components in the genome that can form a hypothetical array by taking advantage of the similarity of strong between DRs (direct repeats). An expanded suffix array is the data structure utilized by the basic programmed Vmatch (Abouelhoda *et al.,* 2004), is employed to find these probable repetitions in huge data sets efficiently. Candidate repetitions are then categorized based on their pairwise similarity, length, and placement. Talented candidates are a length of 23-55 nucleotide, the recap homology of > 80%, and are balance by 0.6-2.5 whiles the recapping size. Following that, repeat both connected based on their distance and separate within the input of DNA sequences, and the consensual repeats are calculated as the greater sequence that appears the very frequently. Additionally, the programme looks for shorter repeat sequence in the flanking areas, which allows for additional gaps. In the end phase, a programme examines the homology of anticipated spacer sequence using MUSCLE (Alkhnbashi *et al.,* 2020). If the pairwise homology among spacers reaches 60%, the corresponding candidates are thrown out. The authors developed CRISPRCasFinder, an evidence-level assessment system based on repeat quantity, identity of spacer pairwise, and recapping conservation. Level 4 & 3 denote extremely promising possibilities, whereas Level 1 denotes improbable systems and Level 2 denotes putative possibilities. CRISPRCasFinder and CRISPRFinder are Perl-based utilities that are accessible in Unix-like operating systems such as MacOS and Linux (https://github.com/dcouvin/CRISPRCasFinder.git), also in the web servers (https://crisprcas.i2bc.paris-saclay.fr/CrisprCasFinder/Index & http://crispr.i2bc.paris-saclay.fr/Server). The output for each array includes data on the coordinates, sequence, and length of each identified spacer, as well as a brief description of the array length, number of spacers, consensus repeat sequence, and coordinates.

2. PILER-CR

PILER-CR (Edgar, 2007) is an open access software for identifying a repeat of CRISPR that depends on the PILER group of algorithms for repeat analysis. Its method begins by looking for hits (local alignments) between the supplied input genome and with itself. These self-alignments thus suggest two possible CRISPR array recap sequences split by a small distance. Following that, the algorithm introduces the concept of a pile. A pile is mean as a stream collection of bases, each of which is enclosed by at least one hit, each of which represents a repeated element. Local alignments connect the piles and serve to form a connection graph of the piles. The piles are the graph's nodes, and each hit between both heaps represents an edge. Respectively linked subgraphs indicate an array candidate that are improved in multiple processes, such as partial match screening and repeated candidate addition. The repeats borders are verified, and if the conservation level is < 90%, the column is removed from the repeats. Finally, Array candidate with extremely identical consensus sequence of repeat (>95 percent) or in nearest proximity (spacer + repeat length) are combined. This software is gotten from http://www.drive5.com/pilercr/ and run the following command to install this package using conda in the MacOS and linux (conda install -c bioconda piler-cr).

3. CRT

The CRT (CRISPR Recognition Tool) (Bland *et al.*, 2007) is designed with a reduced memory footprint in consideration. The aforementioned approaches take a substantial amount of memory because they use powerful data structure, such as extended suffix arrays, that requires a considerable amount of space to achieve their runtime performance. CRT, like the similar tools, generates CRISPR array applicant by searching for repeating sequences. The primary step is to take a k-dimensional sliding window from left into right over the DNA sequence of concern. The method searches for precise pairs within a defined interval i j (,) for each point of the window, which is determined using the user-provided least and greatest predicted lengths of repetitions and spacers. Then, precise pairs are extended to the right and left, with an end user-defined proportion of gaps allowed. Following that, the CRISPR candidate filtered using the following basis: The repeat sequences length must be within an end user-defined spacers and range must be non-recapping and of identical size. Respectively filtered CRISPR candidates are examined for shortened repetitions in the flanking areas to the right and left. If one is discovered, it is included in the final result that the end user receives. CRTs are written in Java & hence environment agnostic. The end user has the option of using a graphical user interface or a command line interface.

4. Other web-based tools and software

In the recent decade to make an understating of the biological system to programmed a in number of web-based tool as in above tools. The other tools are CRISPRDetect ((Biswas *et al.,* 2016), CRISPRdisco (Crawley *et al.,* 2018), CRISPRstrand (Alkhnbashi *et al.,* 2014), CRASS

(Skennerton *et al.,* 2013), MetaCRISPR (Lei & Sun, 2016), CRISPRleader (Alkhnbashi *et al.,* 2016), CRISPRtionary (Grissa *et al.,* 2008).

Databases relevant to CRISPR-Cas

1. CRISPRdb and CRISPRCasdb

The first open access database including CRISPR array from bacterial and archaeal genomes was CRISPRdb (Grissa *et al.,* 2007a). It now supports 232 archaeal genomes in that 870 CRISPR arrays and 6782 bacterial genomes into 8069 CRISPR arrays. CRISPRdb is essentially for CRISPRFinder to discover putative CRISPR and is automatically updated and reflect freshly available genome sequence from the NCBI Reference Sequence Database. The CRISPRdb contains data on (i) the taxonomies, which includes strain data; (ii) the genomic sequences (plasmid or chromosome); and (iii) the CRISPR loci, which includes the entry's IDs, start and finish positions, modification date, and creation date; (iv) the direct repeats' ID, length, and consensus sequence; (v) the spacers' lengths, IDs, and sequences. User can develop their own database of CRISPR arrays and then use BLAST to compare them to open access data. A new database named CRISPRCasdb (Pourcel *et al.,* 2020) was made available alongside the expanded CRISPR-Cas prediction tool CRISPRCasFinder. CRISPRCasdb contains CRISPR array and Cas annotation data for 16,990 prokaryote genomes. CRISPRCasdb can be found at https://crisprcas.i2bc.paris-saclay.fr/MainDb/StrainList (The database recently update) and CRISPRdb may be access in https://crispr.i2bc.paris-saclay.fr/crispr/.

2. CRISPRone

CRISPRone (Zhang *et al.,* 2017) is a website that contains information about CRISPR-Cas system contain 21,186 draught genomes and 11,102 complete. As false-CRISPR arrays focuses by CRISPRone, often known as mock CRISPRs. Furthermore, the web-based server provides services for (i) predicting CRISPR arrays using MetaCRT (Rho *et al.,* 2012), (ii) identifying Cas proteins using HMMER and Hidden Markov Models and, (iii) predicting the anti-repeat, which is part of the tracrRNA and is complementary to a consensus repeat. CRISPRone available in web server at https://omics.informatics.indiana.edu/CRISPRone/index.php.

3. Anti-CRISPRdb

So far, the database (Dong *et al.,* 2018) is the only available database on antiCRISPR proteins (Acr). It is made up of a manual compilation of reported anti-CRISPR proteins and their similarity using open access databases. It allows the user to filter, browse, download, search, and exchange data and possible novel anti-CRISPR protein. Anti-CRISPRdb comprises 106 non-redundant proteins sequence organized into 6 main families: AcrIA, AcrIB, AcrIC, AcrIID, AcrIIE, AcrVIF, & 23 sub-families, comprising AcrID1, AcrIF1-10, Acr IIC1-3, AcrIE1-4, and AcrIIA1-5. Anti-CRISPRdb available in http://guolab.whu.edu.cn/anti-CRISPRdb/.

Classification of CRISPR-Cas

CRISPR-Cas systems must be classified in arrangement to demonstrate the origin and development of CRISPR locus in genome sequence. Unfortunately, the bulk of cas genes are developed fast in comparison to certain other genes in bacterial and archaeal genomes, making simple categorization into separate families difficult. CRISPR-repeats, on the other hand, have been explicitly categorized into families, encapsulating the complete variety of sequences and pseudoknots of CRISPR-Cas system. Despite that CRISPR-repeat categorization influences the development of CRISPR RNA, there is no proof for a made even link between the kind of CRISPR repeat that those proteins and Cas proteins identify. As a result, categorizing CRISPR-Cas system that rely on Cas protein is critical.

1. CRISP Cas classification

The categorization is based on a combination of Cas loci structure and hallmark protein family analysis. In brief, the scientists created a 394 position-specific scoring matrices (PSSM) collection from across entire protein families involved with CRISPR-Cas systems. Using a strict similarity criterion, these position-specific scoring matrices are utilized to look the NCBI reference sequence database for protein sequence from full bacterial and archaeal genomes. The potential loci are expanded up to 5 genes in two directions and confirmed for fullness. As Cas genes implicated in adaptation are shared by varices subtypes, completeness only relates to the effector genes. For the hallmark genes of the various kinds and subtypes, the whole locus was scored with (many) PSSMs. The final categorization was determined using a novel similarity metric between both groups of interference proteins. It is defined as the average of all protein pairings' pairwise normalized similarity across two sets. The pre-existing manual CRISPR categorization was accurately recreated by clustering based on this commonality. Furthermore, a k-nearest neighbor classified based on this homology categorized just 4 of the 1942 locus wrong, achieving an accuracy of 0.998. (Shmakov *et al.,* 2017) found three new class II CRISPR-Cas type V subtypes, everything contains a RuvC-like endonuclease domain, and three type VI subtypes, each containing two HEPN domains anticipated to retain RNase activity, in a comprehensive analysis of draught and complete bacterial and archaeal genomes beside with metagenomic contigs in 2017. The study conducted a thorough comparison of genes biologically connected to CRISPR Cas systems, resulting in the identification and categorization of novel Cas gene families (Shah *et al.,* 2019). Their members are usually found around Type III CRISPR-Cas interfering gene cassette. The research also revealed that over half of the novel accessory genes do not produce CRISPR-associated Rossman Fold (CARF) domains, and their function is unclear. Furthermore, the authors discovered that non-CARF accessory genes are much more varied than CARF counterparts. Eventually, because to the variety of non-CARF genes, more families are expected to be discovered in the future, according to the experts.

2. CRISPRmap

CRISPRmap (Lange *et al.,* 2013) is the first method for classifying CRISPR-Cas system founded on direct repeat sequence and structure of RNA secondary conservation. As a result, it provides a reliable data source for studying the characteristics of CRISPR systems (in comparison to CRISPR subtype evolution). CRISPRmap accepts as input DR sequence and groups them based on sequence and protein structures conservation. Cluster is examined for the existence of a structural motif (four neatly stacked pairs with a hairpin) and child clusters overlap. Those that met these requirements are classified into groups significant sequences homology using Markov Clustering. CRISPRmap was exclusively utilised to investigate the CRISPR arrays co-evolution and the Cas6 and Cas1 proteins. Utilised CRISPRmap to explore the co-evolution of Cas6 proteins and CRISPR arrays and shown that haloarchaeal CRISPR-Cas systems differ from documented systems where the Cas6 protein is functionally defined (Brendel *et al.,* 2014). Similar research in several *Methanosarcina mazei* strains (Nickel *et al.,* 2019) discovered that all *Methanosarcina mazei* strains have at least two CRISPR-Cas systems, with CRISPR-repeats grouped at least two unique Cas6 proteins and into two sequence families. Also, CRISPRmap is utilised to categorise around three hundred CRISPR-repeats found in the metagenome of human gut (Gogleva *et al.,* 2014). CRISPRmap is a web server there at http://rna.informatik.uni-freiburg.de/CRISPRmap/Input.jsp. CRISPRmap application to a large set of over 3500 CRISPR repeats offered a comprehensive review of CRISPR repeat conservation, 40 sequence families, identifying 33 probable conserved structural motifs, and their evolutionary links (Brendel *et al.,* 2014).

CRISPRmap generates types of results for a CRISPR array, or more specifically for the consensus DR sequence of the array: (a) a clustering tree of CRISPRmap-database general agreement DRs and the input sequence, simulating a map of sequence and structural conservation; (b) comprehensive information on all discovered structural patterns; and (c) comprehensive data on all sequence groups.

Prediction of Protospacer Adjacent Motif (PAM) Sequences:

PAM are essential in the CRISPR-Cas machinery's acquisition and interference steps. A particular PAM is inserted to the CRISPR array and cleaved by the effector complex for only a protospacer flanked. This is necessary for distinguishing between non-self and self and, as a result, avoiding self-cleavage. Knowledge of the PAM is required to use a CRISPR-Cas system for biotechnology purposes. A systematic prediction of PAM sequences is thus critical, fundamentally for non-model species. The CASPERpam algorithm (MENDOZA, 2017) is recently detects protospacer containing sequences using BLASTn and provides a confidence score to the prediction. CASPERpam is applied to all bacterial genomes in the NCBI database containing a CRISPRCas system, resulting in the discovery of PAMs for 221 systems. (Shmakov

et al., 2017) gathered 720,391 spacers for this purpose. A BLASTn search across NCBI reference databases (viral, plasmid, and prokaryotic) with a sequence coverage of 95 percent and a coverage constraint of 95 percent yielded 26,364 (3.7 percent) hits for 1049 species. PAMs were then calculated by computing bitwise scores for spacer flanking sequences from a single species. Twelve predicted PAMs were compared to their empirically determined counterparts for validation, and only seven matched or exhibited good correlationThe effectiveness of the authors' technique to recognise a PAM sequence is greatly depending on the amount of protospacer hits and the CRISPR class. As a result, while CASPERpam can serve as a starting place for PAM determination, further experimental confirmation is necessary.

Identification of Target:

The CRISPR-Cas system ensures precise targeting through two processes. The spacers must be nearly precisely complementary to the targeted nucleic acid, and the target must be accompanied by the right PAM, which is particular to the cas genes involved. The targeting efficiency and possible off-targets of well CRISPR-Cas9 system (with defined PAM) in an application setting are of great interest, and numerous tools have been created to examine these characteristics, including Cas-OFFinder (Bae *et al.,* 2014), CCTop (Stemmer *et al.,* 2015), and uCRISPR (Liang *et al.,* 2017). Because they are specialist technologies with a very unique application situation, we will not go into detail about them here, instead focusing on CRISPR be to in general. In the case of recently found CRISPR-Cas systems with undescribed PAMs, target discovery relies on spacer sequence similarity searches. Surprisingly, only one approach for target prediction in general has been established to our knowledge – CRISPRtarget (Biswas *et al.,* 2013). The BLAST is at the heart of CRISPRtarget, allowing a sequence resemblance exploration of user-supplied crRNAs in public or bespoke databases, as well as prospective target sequences, such as virus/phage. Helper information, like the 3′/5′-handle lengths or PAM sequence, can be included if available, to allow for additional BLAST results filter.

Guide RNA design:

A DNA sequence of interest is directly added, altered, or removed inside the genome during genome editing (Wang *et al.,* 2016). CRISPR-Cas9 and other Cas9-like proteins offer various benefits over conventional gene editing technologies, including target design ease, efficiency, low cost, multiplexed editing, and others. Many studies have demonstrated that CRISPR-Cas9 and similar systems are the most effective gene editing methods for a wide range of species and cell types, including humans, monkeys, mice, fruit flies, zebrafish, and pigs (Baliou *et al.*, 2018; Hsu *et al.*, 2014; Sander & Joung, 2014; Wang *et al.*, 2016). CRISPR-Cas9 has become the primary technique for genome editing since 2014, resulting in a significant growth in computational tools for creating highly precise and effective guide RNAs. Several requirements must be addressed in the creation of these gRNAs, including target specificity,

Example is no off-target effects. There are several tools for designing guide RNAs, the most prominent of which are E-CRISP (Heigwer *et al.,* 2014), CRISPR-ERA (Liu *et al.,* 2015), CHOPCHOP (Montague *et al.,* 2014), GuideScan (Perez *et al.,* 2017), and CRISPOR (Haeussler *et al.,* 2016). They all adhere to the same fundamental ideas. The initial stage is to identify potential target areas based on the gene of interest, the application (repression, knockout, or activation. The proposed target locations are then assessed in terms of two goals: minimal off-target activity and high on-target efficiency.

The latter's score is mostly based on positions of mismatch and is a high predictive potential (up to 98 percent reliable). Target efficiency scores are less discriminating. (Haeussler *et al.,* 2016) provides an excellent review of various scores and their performance. These ratings, on the other hand, are exclusively based on experimentally verified off-targeting restrictions. In order to improve off-target prediction systems, recent research (Klein *et al.,* 2018) seeks to understand the mechanical basis of these principles. The authors provide a straightforward biophysical model that incorporates the underlying mechanics of hybridization kinetics. In general, the free energy needed to transition between both the effector complex's metastable states are employed to characterise the model (the progressions of R-loop formation and PAM binding). CRISPR-Cas is already progressed transcend genome editing into and genome cinematography and epigenetic editing (Wang *et al.,* 2016). This progression is reflected in the commend line tool CASPER (MENDOZA, 2017), which look on gRNA outline for non-model organisms, multipopulation analysis (i.e., Editing many organisms in a metagenome by gRNA design), and multitargeting analysis (i.e., simultaneous modification of different sites using a sgRNA).

Conclusion:

The intricate operation and evolution of CRISPR systems can be understood using bioinformatics approaches, and there are now a wide variety of sophisticated computer tools available for CRISPR-Cas investigations. There is no holistic method that predicts, categorises, and fully describes CRISPR-Cas systems as a one-stop solution, however, and none of these can represent or claim to provide an all-inclusive solution for their respective duties. In order to accomplish their unique goals, users must therefore mix several technologies, which necessitates some understanding of the current tools, their capabilities, and their limitations. Because there is no defined format and numerous tools employ bespoke forms to present their data, this workflow design process is frequently made more difficult. Additionally, pipelining many applications is computationally challenging.

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DIABETES MELLITUS- BIOCHEMICAL BASIS, ETIOLOGY AND REGULATION

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Abstract:

Diabetes mellitus is a clinical syndrome characterised by hyperglycemia. A majority of cases of diabetes mellitus suffer from lack of insulin and also may be due to over production of other hormones like hormones of adrenaline, thyroid which are antagonistic to insulin and inadequate insulin-directed mobilization of glucose by target cells. Diabetes mellitus is related with metabolic disorders that can lead to health complications. This review explores diabetes mellitus in terms of its historical standpoint, etiology, biochemical cause, and regulation.

Keywords: blood glucose, regulation, target cells.

Introduction:

Diabetes mellitus (DM) is probably one of the oldest diseases known to man. It is estimated that 366 million people had DM in 2011; by 2030 this would have risen to 552 million [10]. DM is due primarily to lifestyle factors and genetics. The severity of symptoms is due to the type and duration of diabetes. Some of the diabetes patients are asymptomatic especially those with type 2 diabetes during the early years of the disease, others with marked hyperglycemia and especially in children with absolute insulin deficiency may suffer from polyuria, polydipsia, polyphagia, weight loss, and blurred vision. Uncontrolled diabetes may lead to stupor, coma and if not treated death, due to ketoacidosis or rare from nonketotic hyperosmolar syndrome [11-13].

Types and Etiology:

Classification of diabetes mellitus is based on its etiology and clinical presentation. Subsequently, there are four types of diabetes mellitus such as type 1 diabetes (juvenile diabetes), type 2 diabetes (adult-onset *diabetes*), gestational diabetes, and other specific types like asymptomatic diabetes [14]. Type 1 diabetes is said to account for only a insignificant of the utter concern of diabetes in a society nevertheless it is the major type of the diabetes in younger age groups at majority of opulent nations. The incidence of type 1 diabetes is increasing in both rich and poor countries. It is characterised by the destruction of beta cells in the pancreas (auto immune disease) as result insulin is absent or produced in very less amount. Furthermore, a shift towards type 1 diabetes occurring in children at earlier ages is imminent [14]. 85 to 95% of all diabetes in high-income countries are of type 2 accounting for an even higher preeminence in developing countries. It is closely connected with inappropriate usage of insulin by target cells

and tissues. It is presently a customary and critical health issue worldwide. According to WHO, (1994), this hitch has been provoked by speedy ageing inhabitants, rising urban transition, dietary modifications, diminished physical activity and other noxious lifestyle and behavioral standards. Diabetes mellitus and lesser forms of glucose intolerance, particularly impaired glucose tolerance, can now be found in almost every population in the world and epidemiological evidence suggests that, without effective prevention and control programmes, diabetes will likely continue to increase globally (WHO, 1994). In 2010, about 285 million people in the age group 20- 79 were expected to have diabetes globally, nearly 70% of which reside in developing countries. This evaluation is anticipated to rise to around 438 million, by 2030.moreover, by 2030, the number of people with IGT is expected to rise to 472 million, or 8.4% of the adult inhabitants [14]. The majority of patients with the disease have at least one parent with DM.

Diabetes also takes place due to overproduction of other hormones for example hormones of the adrenal and thyroid which are antagonists to insulin. Pancreatic destruction due to pancreatitis leads to absolute insulin deficiency, the excess secretion of epinephrine and thyroxine resulting into breakdown of glycogen in liver. Diabetic coma may occur if insulin is not taken and diet is not controlled.

The patients should have normal psychological affairs .Stress and strain that stimulate the alpha cells of pancreas and adrenal medulla causing the liberation of glucagon and adrenaline which have glycogenolytic effect resulting in increased blood glucose level.

Diabetes can produce symptoms such as polydipsia, polyuria, enuresis, lack of energy, extreme tiredness, polyphagia, sudden weight loss, slow-healing wounds, recurrent infections and blurred vision [5] with severe dehydration and diabetic ketoacidosis if not controlled. Autoimmune type 1 diabetes patients are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, Addison's disease [1].

More than 90%-95% of diabetes patients belong to this type and most of these patients are adults. The increased incidence of type 2 diabetes in youth is mainly due to the change in the lifestyle of the children in terms of more sedentary life and less healthy food. Obesity is the major reason behind insulin resistance which is mainly responsible for type 2 diabetes [3-4]. The ADA recommends screening of overweight children and adolescence to detect type 2 diabetes. The prevalence of obesity in children in on the rise, which is probably the main reason for the increased incidence of type 2 diabetes in the young (30.3% overall increase in type 2 diabetes in children and adolescence between 2001 and 2009) [2]. Diabetes has been detected in patients with various genetic syndromes such as Down syndrome, Klinefelter syndrome, Turner syndrome and Wolfram syndrome [1]

Due to the mild symptoms of type 2 diabetes in the beginning, its diagnosis is usually delayed for years especially in countries where regular checkup without symptoms is not part of the culture. This delay in diagnosis could increase the incidence of long-term complications in type 2 diabetes patients since hyperglycemia is not treated during this undiagnosed period.

In 1922 Banting and Best purified the hormone insulin from the pancreas cows at the University of Toronto leading to the availability of effective treatment for diabetes. Over the years exceptional work has taken place to tackle this growing problem. Conventional medications for diabetes comprise the administration of exogenous insulin. At present glucagon is not normally incorporated in treatment since it does not conserve its chemical properties at room temperature and also due to diabetic patients are nevertheless able to generate. It is widely reported that oral delivery is the most convenient administration route. However, insulin cannot be well absorbed orally because can be rapidly degrade via enzymatic cleavage in the gastrointestinal tract.

The exhausting effects of diabetes mellitus include diverse organ failures, progressive metabolic disorders such as retinopathy, nephropathy, and neuropathy (Piero, 2006). Diabetics are escorted by risk of cardiovascular, peripheral vascular and cerebrovascular diseases. Various pathogenetic processes are associated with the development of diabetes, including destruction of pancreatic β-cells. Early detection through screening programmes and the availability of safe and effective therapies reduces morbidity and mortality by preventing or delaying complications

Blood glucose and regulation

Glucose is carbohydrate mazuma of the body. The brain and other tissues are dependent on blood glucose for energy. The fasting blood glucose level is between 80-100 mg/dl of blood. Following eating meal blood glucose level normally rises to 130-140 mg/dl at 1 hour but returns to normal level 2 hours after the meal. The raise in the blood glucose above the normal level is called hyperglycemia and hypoglycemia presents decreased blood glucose concentration.

Regulation

Auto regulation: The blood glucose level in normal health regulates itself. As blood glucose tends to increase glycogenesis is accelerated and utilization of glucose by tissues is increased resulting in fall in blood glucose level. The reverse occurs as the blood glucose level tends to fall.

Hormonal control of blood glucose level

Many hormones such as Insulin, glucagon, epinephrine, glucocorticoids, thyroxine, and growth hormone play a significant role in the regulation of blood glucose level.

Insulin is a hypoglycemic hormone that lowers blood glucose level through various means by increasing the rate of glycolysis, glycogenesis, and HMP shunt and by lipogenesis by the uptake of glucose by adipose and liver cells for conversion into fat.

Glucagon it has impact exactly opposite to that of insulin. It evokes rise in the amount of glucose in blood by increasing glycogenolysis by activating the enzyme phosphorylase. It enhances gluconeogenesis from amino acids and lactate. Insulin and glucagon may be thus regarded antagonists.

Other hormones mentioned above also have hyperglycemic effect.

Regulation by kidney

If blood glucose level is 160-180% glucose is excreted in urine. This value referred to as renal threshold for glucose**.**

The proportion of calories in diabetics

The universe is struggling with increased prevalence of obesity, diabetes, and associated metabolic disorders in children and adults. The primary reason for this surplus occurrence is by virtue of increased calorie consumption on a background genetic predisposition. Diabetes mellitus is caused by the deficiency in the secretion of insulin. The various predisposing factors are heredity, age, sex, obesity, stress.

Diet: the patient should follow the diet schedule prescribed by the physician. The calorie requirement should be about 5% less than the actual requirement for the patient's height and ideal body weight.

The primary goal in the management of diabetes is to achieve as near normal regulation of blood glucose (postprandial and fasting) as possible.

The proportion of protein, carbohydrate and fats in the diet

The proportion of calories derived from carbohydrate, fats and proteins in the diet will depend on the type of diabetes as indicated below

Proteins: Due to negative nitrogen balance in diabetics they should reciew about twice as proteins as normal subjects. The protein should be of high biological value and provide 20 to 25% of the calories in the diet. Protein should be a supplement to vegetables, fruits and whole grains in a meal, not the entire meal. Lean protein with each meal (8-12 oz/day) can be included in the diet.

Carbohydrates: The daily requirement of carbohydrates should be 40% of the calories to prevent formation of ketone bodies. The carbohydrate intake should exceed 40% otherwise it is difficult to control blood sugar level. Carbohydrate intake should emphasize nutrient dense carbohydrate sources that are high in fiber, including vegetables, fruits, legumes, whole grains, as well as dairy products. Patients with DM should consume 20 to 35 g of fiber from raw vegetables and unprocessed grains.

People with diabetes and those at risk are advised to avoid sugar-sweetened beverages (including fruit juices) in order to control glycemia and weight and reduce their risk for

cardiovascular disease and fatty liver and should minimize the consumption of foods with added sugar.

Fats: fat quality appears to be far more important than quantity. Recent studies have found that decreasing the amount of saturated fatty acids and trans fatty acids, Eating foods rich in long-chain n-3 fatty acids, such as fatty fish (EPA and DHA) and nuts and seeds (ALA), is recommended for diabetics. Replacing high trans-fat partially hydrogenated vegetable oils, animal fats and tropical oils with healthier oils and foods higher in unsaturated fats — monounsaturated and polyunsaturated fatty acids found in vegetable oils like sunflower and safflower oil, soybean oil, corn oil is recommended [6-7].

In general, saturated fats are discouraged because they increase LDL-cholesterol and total cholesterol concentrations. Diets high in saturated fats have been implicated in an increased risk of cardiovascular disease.

Exercise for individuals with diabetes has many benefits for most, benefits out weight risks. Exercise and resistance training may improve glycemic control [9].

Chromium intake and diabetes

Chromium is a common element in the earth's crust and seawater. It is a critical cofactor in the insulin action and deficiency results in hyperglycemia. Trivalent chromium is found in a wide range of foods, including egg yolks, whole-grain products, cereals, coffee, nuts, green beans, broccoli, meat, and some brands of wine and beer. A few studies have reported beneficial effects of chromium supplementation on the diabetes and glycemic control.

Even zinc is required for the synthesis of insulin and plays an important role in maintaining sugar level along with chromium.

Conclusion:

Diabetes mellitus is the epidemic of the century and without effective diagnostic methods at an early stage, diabetes will continue to rise. This review focuses on the types of diabetes and the criteria to be used for diagnosis of diabetes. Furthermore, our advanced knowledge of the association between medical genetics and the chronic complications of diabetes will provide an additional advantage to delay or eradicate these complications that impose an immense pressure on patient’s quality of life and the significantly rising cost of health-care services. The cornerstone diabetes management is a healthy diet**,** increased physical activity and maintaining a healthy body weight. Oral medication and insulin are also frequently prescribed by the physician to help control blood glucose levels. Further research is still needed to define the optimal macronutrient content for fat (SFA, MUFA, and PUFA), protein, and carbohydrate to attain the most beneficial lipid and lipoprotein profile in the general population and in those with diabetes at increased risk for CVD.

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LEI DETECTION TECHNIQUES AND THEIR MEDICO-LEGAL ASPECTS

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Abstract:

When a person tells lies there are numerous physiological changes in the body. Such changes may be captured by using modern technologies in computers. Great efforts have been made to use newer technologies such as Magnetic Resonance Techniques. The concept of lying and the ability to do so have reached a new level with technological advances that have moved lie detection from the realm of fire and water to EEGs, FACS, and functional MRIs. The present chapter examines the practice of various lie-detection techniques in the past and present and their medico-legal perspectives.

Keywords: Lie, Lei detection, Mechanical lie detector, Brain mapping,

Introduction:

Since the beginning of human civilization lying has been a part of everybody's life. It has been a part of human civilization and continues for ages as a survival strategy. Similarly, lie detection is also an age-old practice. It is an integral part of a criminal investigation. It may be defined as an assessment of a verbal statement with the goal to reveal possible intentional deceit. Police officers are challenged by deception, especially in the determination of facts in crimes that have been committed. Judges and lawyers seek justice in legal disputes. It is useful not only in criminal and legal systems but also in the medical profession for proper diagnosis and treatment.

Early methods of Lei detection:

Ford (2006) reported that one of the first methods to prove the veracity of a statement uttered by the accused was described in China circa 1000 BC.[1] The person suspected of lying was required to fill his/her mouth with a handful of dry rice. After a while, she/he was to spit out the rice. If the expectorated rice remained dry, the suspect was found guilty of fraud. This method was based on the physiological principle and the assumption that experiencing fear and anxiety is accompanied by decreased salivation and a dry mouth. The works of contemporary authors (Matsumoto, 2009; Praško, 2011) imply that fear paralyzes us and is physically reflected in an increased heart rate and a mental sense of hopelessness.[2] The somatic expression of anxiety and fear include changes in behaviour associated with the feeling of a dry mouth. The symptomatology is similar to manifestations of depression, panic disorder, and the like (Höschl, Libiger, & Švestka, 2004).[3] Given the fact that the aforementioned knowledge about the

physiological manifestations of anxiety was not known at that time and thus not taken into account, the majority of prisoners, regardless of whether they had actually committed a crime or lied, were executed. Several centuries later Erasistratus, a Greek physicist and physician (300-250 B.C.), tried to detect deception by measuring the pulse. This same technique re-emerged as a part of testing with polygraphs in 1921 (Trovillo, 1939).[4]

The trial by ordeal method

The historical writings of various European countries more often mention a technique known as *trial by ordeal* - or the *Judgments of God* (Apfel 2001; Holák, 1974; Sullivan, 2001).[5] This was another method used by authorities in the interest of detecting lies and finding the truth. It was used to prove the truth of a claim of an accused person by a specific act that the person had to go through. Based on its favorable or un-favorable outcome, the claim was accepted as true or false.

The rationale (and hence the court's argument) was based on the belief that God would not let a righteous man suffer and injustice prevail. For example, in the territory of present-day Slovakia, the first courts were established in the 11th century. They concerned either a one-sided substantiation of the truth by the accused person or a double-sided one when one was subjected to the judgment of God (Holák, 1974).[6] The one-sided judgment of God was conducted by a water test or a fire test. The water test was carried out by using either hot or cold water. When using the hot water test, the accused was ordered to place the hand into a cauldron with boiling water and hold it there for a specified time. If the hand in boiling water showed no traces of scalding or small blisters, it represented a sign of the accused person's claim was true. A variation of this test involved the accused retrieving a ring or stone out of the cauldron of boiling water.

The test based on cold water included throwing the accused person into the water in a roped sack. If the tested person emerged at the surface in a short time, it signified that "not even water accepts him/her" – or more precisely – servants of the devil (hence liars too) rejected baptism and that is why water cannot accept him/her (Sullivan, 2001, p. 213).[7]

Regarding the hot water method, there were individuals who doubted the credibility of this procedure. In 1593, in the Netherlands, the court turned to a university and asked for an examination of the water test to determine its appropriateness as a lie detection technique. In this case, rationality won and the test was disapproved (Apfel, 2008).[5] However, the application of the test with cold water remained popular until the 18th century as evidenced by court records in Vojtka on the Danube, when 70 women were subjected to this test (Holák, 1974).[6]

In the case of using fire as a proving method, the accused was compelled to carry a hot piece of metal for a certain distance or walk across burning embers. The accused was considered innocent if either no wounds appeared or they healed quickly.

Sometimes the court turned to the use of the consecrated meal. The examining person was a priest who, at the end of worship, gave the accused a piece of dry bread and a piece of hard sheep's cheese. The accused was exonorated if he or she managed to swallow in one bite without difficulty. However, if the person choked or suffocated, the test brought a guilty verdict. There are some similarities between this method and the Chinese use of rice. In China, as well as in Europe, people attempted to identify lies through methods of using their mouths. However, the Chinese method's verification was based on objective knowledge of physiological manifestations of fear – in the case of fear, the mouth stays dry.

Methods based on God's judgment ceased to exist past the 15th century, and only the cold water test mentioned above remained. It was used mainly for the substantiation of witchcraft. People gradually realized that the guilt or innocence of a person could not be detected using various "experiments" based on magic or divine forces possessing the power to protect the innocent. The change in the assessment of truth and deception came gradually through the development of various scientific fields.

Phrenology and graphology

In 1870, Franz Joseph Gall discovered a new possibility of detecting deception through the recognition the of emotions of the accused. The theory was elaborated and further improved in cooperation with his pupil Spurzheim. The point of their interest wan as an examination of specific areas of the brain assuming the existence of relations between different abilities and skull shape (Rafter, 2005).[8] The main ideas of their theory pointed to the brain as the central organ of the mind which can perceive individual emotions such as emulousness, ambition, destructiveness, and, among many others, the tendency to lie and to engage in criminal behavior. The more active parts of the brain are well recognizable from the contour of the skull (these areas were more convex or concave). It was assumed that the relative size of each area can be enlarged or reduced by training and self-discipline. Gall became a pioneer in mapping the human skull and this newly-created scientific discipline was named phrenology. Gall often made public appearances demonstrating various criminals with shaved heads and emphasizing the "Anomaly" on the skulls. Through phrenology, he tried to determine liars randomly chosen from the audience. His services were also occasionally used in legal disputes to determine which party was lying.

In the field of criminology, phrenology helped to spread the belief that delinquent behavior (together with lying) should be the subject of scientific study. It strengthened the medical model of criminal behavior according to which the behavior of some perpetrators may be affected by brain malfunctions. By virtue of this idea, many crimes were reassessed saving a multitude of mentally ill people from being unfairly sentenced (Trovillo, 1939).[9] Although phrenology fell into oblivion and was discredited, Gall's work rendered an important service by reminding researchers

that the human body is affected by environmental factors and together they build an entity of mutual relations (Hall & Lindzey, 2002).

Simultaneously with phrenology, graphology began to spread and in 1875 started to be considered a useful scientific method of lie detection (Schönfeld, 2007).[11] Its origins are associated with an effort to detect forged signatures which led to the scientific analysis as we know it nowadays. Its founder, J. H. Michon, assumed that some peculiarities of handwriting may relate to certain personality traits. Following the analysis of handwriting, graphology attempts to identify a personal writing movement through which the nature of the writer may be manifested (Schönfeld, 2007).[11] The excitement around graphology as a method of lie detection ended after the First World War. During the war graphology was deemed an appropriate means of verifying the authenticity of documents and signatures. However, graphology was not acknowledged as an appropriate tool for lie detection. Nowadays, this method is used in various areas such as employment profiling (to do a personality profile) or psychological analysis (used alongside other projective personality assessment tools), (Poizner, 2012; Thomas, 2001).[12]

Modern methods of Lie detection:

1. The polygraph (Mechanical Lie Detector)

A polygraph is a machine in which the multiple ("poly") signals from the sensors are recorded on a single strip of moving paper ("graph"). During this procedure or process, there is measurement and recording of different parameters such as blood pressure, pulse, respiration, and skin conductivity while a person is asked and answers a series of questions. It is also known as Lie Detector or Mechanical Lie Detector. It is based on the simple principle that there will be normal physiological changes when a person is trying to hide lies. Thus, when a person tells lie, he shows involuntarily emotional and mental changes, and these changes are recorded and analyzed in a polygraph. The examinee must have information about what he/she is going to experience and how physiological responses show truth and lie. This will lead to a better test experience. The examiner knows when psychological changes occur and correspondingly the polygraph records those changes. This section is an interview process and it’s not like an interrogation.

Polygraph examination consists of three phases:-

(a). Pre-test phase: It is the most important part of the test. During the pre-test phase, the examiner tries to communicate with the examinee. In this part, the examiner collects information. Because it is necessary for the examiner to know the examinee and for the examinee to be tested justly. Besides, no test is taken until a person is volunteer for the test. The volunteer should sign the forms of voluntary before the per-test starts. There are basically three kinds of questions for asking namely (a) irrelevant questions - Irrelevant questions are formulated to demonstrate ordinary answers, (b) relevant questions - Relevant questions are for the administration of

polygraph examination, and (c) control questions - Control questions used by the examiner when the examinee answered equivocally.

Figure 1: The polygraph (Mechanical Lie Detector)

(b). In–Test phase: This phase is also known as Chart Collection or Polygraph Examination. The actual polygraph examination takes place during this phase. Just before beginning the examination, the blood pressure cuff will be inflated to a pressure of 60 mmHg. The examiner will then ask the examinee the series of questions that were formulated and reviewed during the pre-test interview. This series of questions will be asked a minimum of three times. As the examinee answers the questions, his or her physiological data are continuously collected, measured, and recorded by the polygraph instrument.

(c). Post–Test phase: During this phase, there is the analysis of the collected graphs data and so this phase is also known as the Data Analysis phase. The examiner evaluates each question separately. Often, in order to evaluate the test, the examiner applies a computer algorithm and a numerical scoring system. Then, the examiner decided if the examinee was telling the truth or lying and even the test was result-less.

The result may be one of the following three:-

(a). No deception: The examinee is telling the truth.

(b). Deception indicated: The examinee is not telling the truth.

(c). Inconclusive: The evaluation of the examinee's physiological data is inconclusive.

The whole process usually takes about 1 to 2 hours.

Medico-legal aspects:

The polygraph is widely considered unreliable in scientific circles, partly because its effectiveness depends heavily on the intimidation skills of the interrogator. What a polygraph actually measures is the stress of telling a lie, as reflected in accelerated heart rate, rapid

breathing, rising blood pressure, and increased sweating. Sociopaths who don't feel guilt and people who learn to inhibit their reactions to stress can slip through a polygrapher's net.

2. Trans-cranial Magnetic Stimulation (TMS):

This technique uses a pulsing electromagnet to influence the brain. It was developed by Inga Karton and Talis Bachmann, both from Estonia.[15] Those studied were asked to tell researchers the color of an object on a computer screen, but they were allowed to lie or tell the truth as they liked. When the left half of the DLPFC (The Dorsolateral Prefrontal Cortex) was stimulated with TMS, those studied tended to lie slightly more. Stimulating the right half had the opposite effect.

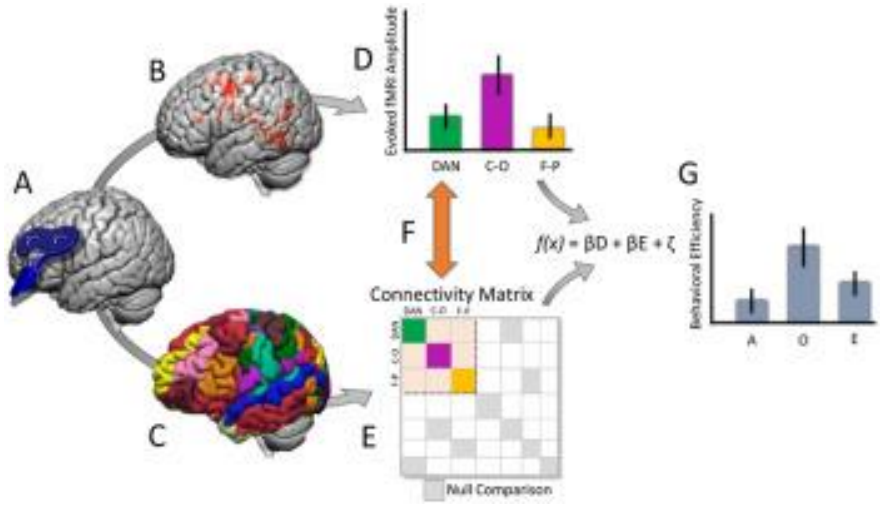

Figure 2: Trans-cranial Magnetic Stimulation

Image courtesy – ScienceDirect.com: Available from: https://ars.els-cdn.com/content/image/1-s2.0-S2665945X21000139-ga1.jpg

3. Functional magnetic resonance imaging (fMRI):

This functional magnetic resonance imaging technique enables the detection of very minute anatomical as well as functional changes in the brain by using a very powerful magnetic field and radiofrequency pulses. This is done by analyzing the blood flow areas of the brain involved in deception.

As Prospects of fMRI as a Lie Detector states, fMRIs use electromagnets to create pulse sequences in the cells of the brain. The fMRI scanner then detects the different pulses and fields that are used to distinguish tissue structures and the distinction between layers of the brain, matter type, and the ability to see growths. The functional component allows researchers to see activation in the brain over time and assess efficiency and connectivity by comparing blood use in the brain, which allows for the identification of which portions of the brain are using more oxygen, and thus being used during a specific task. This is called the Blood Oxygen Level Dependent or BOLD hemodynamic response.[16]

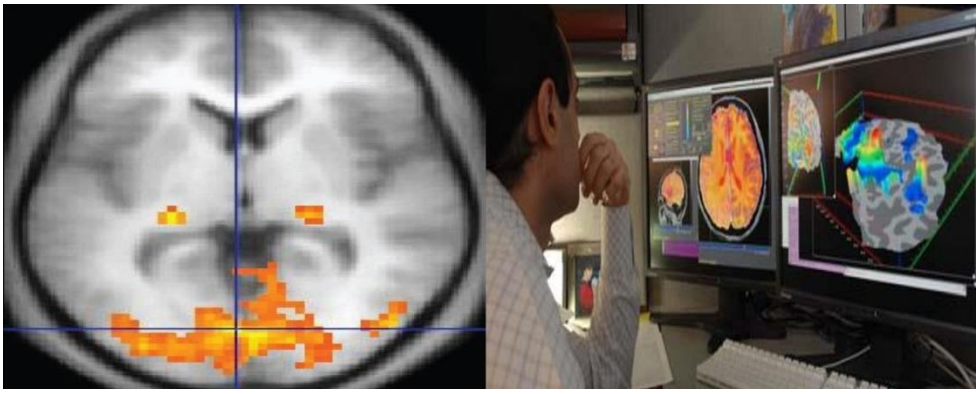

Figure 3: Functional magnetic resonance imaging

An fMRI image with yellow areas showing increased activity compared with a control condition. (It measures brain activity detecting changes due to blood flow.): Image Courtesy – Wikipedia available from: https://en.wikipedia.org/wiki/Functional_magnetic_resonance_imaging

FMRI data have been examined through the lens of machine learning algorithms to decode whether subjects believed or disbelieved statements, ranging from mathematical, and semantic to religious belief statements. In this study, independent component features were used to train the algorithms, achieving up to 90% accuracy on predicting the response of a subject, when prompted to indicate with a button press whether they believed or disbelieved a given assertion.[17]

Medico-legal aspects:

Historically, fMRI lie detector tests have not been allowed into evidence in legal proceedings, the most famous attempt being Harvey Nathan's insurance fraud case in 2007.[18] This pushback from the legal system may be based on the 1988 Federal Employment Polygraph Protection Act which acts to protect citizens from incriminating themselves and the right to silence. The legal system specifically would require many more studies on the negative false rate to decide if the absence of deception proves innocence. The lack of legal support has not stopped companies like No Lie MRI and CEPHOS from offering private fMRI scans to test deception.

There is potential to use fMRI evidence as a more advanced form of lie detection, particularly in identifying the regions of the brain involved in truth-telling, deception, and false memories.[19] False memories are a barrier to validating witness testimonies. Research has shown that when presented with a list of semantically related words, participant recollection can often be unintentionally false and additive of words that were not originally present. This is a normal psychological occurrence but presents numerous problems to a jury when attempting to sort out the facts of a case.

fMRI imaging is also being used to analyze brain activity during intentional lies. Findings have shown that the dorsolateral prefrontal cortex activates when subjects are pretending to know information, but that the right anterior hippocampus activates when a subject presents false

recognition in contrast to lying or accurately telling a truth. This indicates that there may be two separate neural pathways for lying and false memory recall. However, there are limitations to how much brain imaging can distinguish between truths and deceptions because these regions are common areas of executive control function; It is difficult to tell if the activation seen is due to the lie told, or something unrelated.

Future research aims to differentiate between when someone has genuinely forgotten an experience and when someone has made an active choice to withhold or fabricate information. Developing this distinction to the point of scientific validity would help discern when defendants are being truthful about their actions and when witnesses are being truthful about their experiences.

4. Positron emission tomography (PET) scan:

A PET Scan (or Positron Emission Tomography) is a non-invasive, diagnostic examination that finds information about the activity of different parts of the body.[20] Those parts of the body that are the most active need energy, and the energy that it uses is sugar (also called glucose). A PET scan uses a specially created substance that the body thinks is sugar, and takes up into the cells. This substance is called a 'tracer', and it is almost exactly like sugar but has a small radioactive part attached to it. The images are based on the detection of radiation from the emission of positrons (positively charged electrons) from this radioactive tracer. The subsequent images created are used to evaluate a variety of diseases, with the most common use being whole-body imaging of cancer.

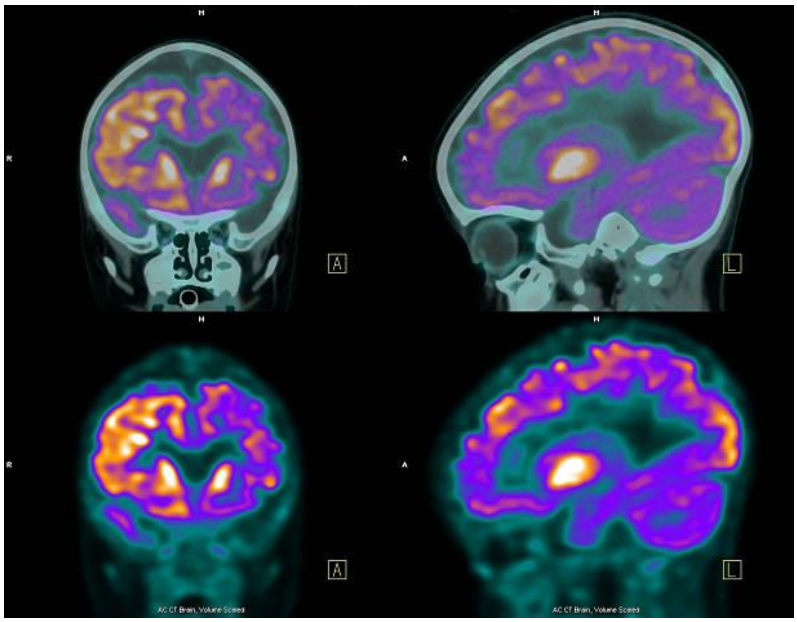

Figure 4: Brain images of PET Scan showing different areas of hyperactivity

PET scans are beneficial as they demonstrate the biochemical changes in the body, whereas a CT or MRI scan identifies anatomical changes. A PET Scan therefore helps to identify

problems at the level of their activity and function, which might change long before any changes in body structure (such as a tumour) become apparent. This allows for earlier diagnosis and more effective treatment of diseases such as cancer, and also more detailed imaging of other conditions. There is little risk involved with the intravenous administration of the radioactive "tracer" as the tracer has a short decay time of only a few hours and is quickly removed from the body.

5. Brain Fingerprinting (EEG wave):[21]

It is a new technology to identify the preparatory of a crime by measuring the brain wave responses to crime-relevant words or pictures presented on a computer screen. Brain Fingerprinting is based on the principle that the brain is central to all human acts. In a criminal act, there may or may not be many kinds of peripheral evidence, but the brain is always there, planning, executing, and recording the crime. The fundamental difference between a perpetrator and a falsely accused, innocent person is that the perpetrator, having committed the crime, has the details of the crime stored in his brain, and the innocent suspect does not. This is what Brain Fingerprinting detects scientifically.

The person to be tested wears a special headband with electronic sensors that measure the electroencephalography from several locations on the scalp. In order to calibrate the brain fingerprinting system, the test is presented with a series of irrelevant stimuli, words, and pictures, and a series of relevant stimuli, words, and pictures. The test subject's brain response to these two different types of stimuli allow the tester to determine if the measured brain responses to test stimuli, called probes, are more similar to the relevant or irrelevant responses.

Figure 5: Brain Fingerprinting Technology

The technique uses the well-known fact that an electrical signal known as P300 is emitted from an individual's brain approximately 300 milliseconds after it is confronted with a stimulus of special significance, e.g. a rare vs. a common stimulus or a stimulus the proband is asked to count. The novel interpretation in brain fingerprinting is to look for P300 as a response to stimuli related to the crime in question e.g., a murder weapon or a victim's face. Because it is based on

EEG signals, the system does not require the taste to issue verbal responses to questions or stimuli. Brain fingerprinting uses cognitive brain responses, brain fingerprinting does not depend on the emotions of the subject, nor is it affected by emotional responses. Brain fingerprinting is fundamentally different from the polygraph (lie-detector), which measures emotion-based physiological signals such as heart rate, sweating, and blood pressure. Also, unlike polygraph testing, it does not attempt to determine whether or not the subject is lying or telling the truth.

Advantages & Disadvantages:

It is more useful than the witness testimony in crime investigation as witness testimony provides an indirect and subjective account of this record. The records stored in the brains of suspects are brought into the realm of scientific scrutiny and objective investigation. Brain fingerprinting eliminates the chances of deception on the part of the witness. This technique is not 100% true in every case as it only detects information in the brain of a person. It may be that an innocent person may be knowing about the crime as a third person or listener or maybe he may be present at the crime scene. Human memory is imperfect and limited. As the technology is costly, not all people can use it.

Conclusion:

Lie detection is a part of numerous criminal, medical or legal professions. Police officers are challenged by deception especially in the determination of facts in crimes that have been committed. Judges and lawyers seek justice in legal disputes and medical specialist demand the truth for accurate diagnosis and appropriate treatment of patients. As science advances many sophisticated newer techniques will be available in the coming days.

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NEEM (*AZADIRACHTA INDICA*): MEDICINAL KALPAVRIKSHA

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Abstract:

Azadirachta indica, also known as neem, Due to its numerous medical virtues has gained fame on a global scale recently. Neem has become popular in modern medicine due to its extensive use in Ayurveda, Unani, and homoeopathic treatments. To better understand the metabolic process and its impact on the human body, traditional medicine and evidence-based medicine are being combined in global health and medical practise. Use of supplementary therapies like phytotherapy is one illustration. Due to its numerous health benefits, *Azadirachta indica*, also known as neem, a tree native to India and Myanmar, is sometimes referred to as "The village pharmacy" or "Divine tree." Neem-derived extracts have recently been demonstrated to be effective in a variety of applications, including insect repellant, supplements to reduce inflammation, diabetic management, and even to combat cancer. From various neem plant components, more than 140 distinct chemicals have been discovered. The traditional use of the neem tree's leaves, blossoms, seeds, fruits, roots, and bark for the treatment of inflammation, infections, fever, skin conditions, and dental problems includes all of these parts. Neem leaf's therapeutic benefits have been specifically discussed. Immunomodulatory, anti-inflammatory, antihyperglycemic, antiulcer, antimalarial, antifungal, antibacterial, antiviral, antioxidant, antimutagenic, and anticarcinogenic activities of neem leaf and its components have been proven.

Keywords: Neem, phytotherapy, human diseases, phytochemicals

Introduction:

Azadirachta indica is also referred to as the margosa tree or Indian neem. The World Health Organization defines "well health" as a state of mental and physical health that is untouched by any ailment (Arumugam *et al.*, 2014). It has been widely used in ayurveda, unani, and homoeopathic medicine since the beginning of time. "Nimba," which later became "Neem," is a Sanskrit word that meaning "good health and the tree are referred to as "Sarvaroga nivarini," which means "cure all ailments." In Ayurveda, neem is known as "Arishtha," which means "reliever of ailments." Due to the tree's healing properties, it is still known in India as the "Divine tree" or the "village pharmacy." More than 80% of the population is said to be dependent on

medicinal herbs, especially in developing nations. Neem is a native medicinal plant to India, and all parts of it, including the fruit pulp, bark, leaves, seeds, blooms, and roots, have therapeutic properties. One example of phytotherapy in complementary medicine is neem. Each part of the plant has been used in Indian medical systems such as Ayurveda and Unani, and it is now widely used in modern medicine. In Ayurvedic literature, neem is well known for its medicinal properties, namely for its cold, bitter, astringent, and caustic bark. It is used to cure a variety of other diseases as well, including worm infestation, fever, coughing, and tiredness. Along with treating wounds, kapha-vitiated conditions, nausea, skin issues, excessive thirst, and diabetes, it also addresses these other conditions.

Chemical elements found in the leaves are said to be useful for treating eye conditions and making insect poisons along the bark. Both Vatik disorder and leprosy are treated by it. Its fruits are pungent, antihemorrhagic, antihelminthic, and bitter. Biological Activity and Neem Compounds From various neem plant components, more than 150 distinct chemicals have been discovered. The compounds have been divided into two main categories: isoprenoids (like diterpenoids and triterpenoids containing protomeliacins, limonoids, azadirone and its derivatives, gedunin and its derivatives, vilasinin type of compounds, and C-secomeliacins such as nimbin, salanin, and azadirachtin) and non-isoprenoids (such as proteins, carbohydrates).Nimbidin is the source of the crudely derived bitter ingredient. Azadirachata, chemistry, and therapeutic characteristics the oil from the seed kernels of A. indica, which has several biological properties. From this basic idea, some tetranortriterpenes, such as nimbin, nimbinin, nimbidinin, nimbolide, and nimbidic acid, have been isolated. These compounds have biological properties similar to those of neem, pharmacological properties similar to those of neem extracts, clinical studies similar to the neem contains substances that have anti-inflammatory, anti-arthritic, antipyretic, hypoglycemic, anti-gastric ulcer, spermicidal, anti-fungal, anti-bacterial, diuretic, anti-malarial, anti-tumor, and immunomodulatory properties. Therefore, the interest of different communities and researchers, to several parts of the Neem to produce extracts. Out of all, the oil appears to be the most widely used portion (Deng *et al.*, 2013, Patel *et al.,* 2016). Over time, these proposed complexes of herbs and plants have been in more detail studied. Results have found that many of these herbs and plants contain several compounds mainly of the following families: flavonoids, catechins, anthocyanins, quercetins, saponins, tannins, limonoids, gallic acids, and other minorpolyphenols;all known to have biological effect (Nagini, 2014; Alzohairy, 2016; Heyman *et al.*, 2017).

Chemistry of Neem Compounds Natural compounds present in neem are triterpenes or limonoids. New limonoids are still being discovered in neem. Azadirachtin, salannin, meliantriol and nimbin are well known. The bitter constituent, the nimbin contains an acetoxy, a lactone, an ester, a methoxy and an aldehyde group. Nimbidin contains sulphur.

1. Bark: A clear, bright amber-colored gum that is accumulated in tiny tears or fragments is exuded by the bark. Margosine is an unpleasant alkaloid found in it. In modest amounts, leaves also contain bitter compounds that are far more soluble in water. This material is a resin hydrate. 10% to 31% of a yellow, bitter fixed oil with a strongly unpleasant, caustic flavour can be found in seeds. Stearic, oleic, and a trace amount of lauric acids make up the volatile fatty acids found in the bark. Nimbin, Nimbinin, Nimbidin 0.4%, and Nimbidin 0.2% are all produced by the trunk bark. Along with tricyclic diterpenoids, tetracyclic triterpenoids and their derivatives have been identified from the stem bark.
2. Flowers: Flowers have been found to contain a flavonoid. Nimbicetin is identical to kaempferol. In the dried bark the same bitter components as in the seed oil have been found and in the pericarp of the fruit a bitter principle bakayanin was found.
3. Neem oil: Sulfur (0.427%), an extremely bitter yellowish compound derived from the oil's alcohol extract and thought to be an alkaloid, resins, glucosides, and fatty acids are all present in neem oil. 3.4. Seeds The seeds include gedunin, 7-desacetylgedunin, desace-tylnimbin, and azedarachtin, which are all meliacins. Nimbidin, Nimbin, and Nimbinin, which also occur in stembark, are primarily found in seed oil.
4. Toddy: The toddy or sap contains glucose, sucrose, gums and colouring matter.

Medicinal uses:

1. **Ayurveda:** Neem tree has occupied a prominent place in the traditional Ayurvedic medicine in India from time immemorial. Neem bark, leaf extracts and neem oil have been under use as folk medicine to control various problems viz., leprosy, intestinal helminthiasis, constipation, etc. Further, it plays vital role in treating rheumatism, chronic syphilitic sores and indolent ulcers. Neem oil is well known to control various skin problems. Bark, leaf, root, flower and fruit together cure blood morbidity, biliary afflictions, itching, skin ulcers, burning sensations and pthysis. The root bark and young fruits are used as an alternative, antiperiodic and as a tonic. Green twigs are used as toothbrushes for cleaning teeth and as a prophylactic for mouth and teeth complaints. The bark, gum, leaf and seed are used in snake bite and scorpion sting. The bark is used as a bitter tonic, astringent, antiperiodic, antipyretic and against nausea and vomiting. Gum is demulcent tonic in catarrhal affections. Leaves are used as poultice for boils. Decoction of leaves used as an antiseptic in ulcers and eczema. Dry flowers are stomachic. Seed oil is a stimulant, antiseptic, alterative in rheumatism and skin diseases. Berries are purgative, emollient and anthelminthic. An extract of leaves is used in toothpastes. Neem oil is effective in the treatment of leprosy and skin diseases.
2. **Homoeopathy:** used against rheumatic pains. Pain in sternum and ribs, in the extremities and aches in hands and toes. Also used against eczema, pemphigus and scabies.

3. **Unani:** Neem finds use as a resolvent and blood purifier. Leaves expel wind, heal ulcers in urinary passages. Used as an emmenagogue and in skin diseases. Fruit is used as an astringent and in leprosy and bronchitis.
4. **Immunostimulant activity:** The aqueous extract of leaf and bark has been shown in numerous studies to have anticomplementary and immunostimulant action. It has been demonstrated that neem oil has the ability to selectively activate immunological systems within the cell, resulting in an improved response to a subsequent mitogenic or antigenic assault.
5. **Hypoglycaemic activity:** Neem leaf extracts have demonstrated excellent efficacy in lowering blood sugar levels and preventing hyperglycemia brought on by both adrenaline and glucose. Recently, both normal and diabetic rabbits induced with alloxan showed hypoglycaemic effects with leaf extract and seed oil.
6. **Antiulcer effect:** Aqueous extracts of neem leaf and bark have extremely powerful antiacid secretory and antiulcer action. Nimbidin significantly reduced the incidence of duodenal ulcers caused by histamine or cysteamine as well as acetylsalicylic acid, indomethacin, stress, or serotonin-induced gastric lesions.
7. **Antimalarial activity**: Neem seed and leaf extracts are effective against both chloroquin-resistant and sensitive strain malarial parasites. One of the neem's components, "gedunin" (a limonoid), is as effective as quinine against malaria. Malaria is one of the pandemic diseases causing millions of deaths every year in India and several other countries. China has adopted neem in a big way to reap the antimalarial effects of neem. The antimalarial formulation "Quinahausa" prepared in China will be available in India as well. Neem oil treated mosquito nets and mosquito-repellent cheap tablets are also becoming popular, due of growing problems of resistance to conventional treatments, it is becoming more and more difficult to control malaria. Clinical trials have been conducted to check the efficacy of neem extracts to control hyperlipidemia in a group of malarial patients severely infected with P. falciparum. The lipid level, especially cholesterol, was found to be lower during therapy when compared to non-malaria patients.
8. **Antifungal activity:** Neem has long been thought to be useful against several fungi that infect the human body. The athlete's foot fungus, which affects the skin, hair, and nails, the ringworm, which attacks the feet's skin and nails, the fungi that grow in the lungs, bronchi, and mucous membranes, as well as the normal mucous flora that can become out of control and cause lesions in the mouth (thrush), vagina, and other places, are some of the significant fungi that neem preparations have been found to Neem leaf and oil seed extracts are effective against several fungus, including Candida, Trichophyton, Epidermophyton, Microspor, and Trichosporon.

9. **Antibacterial activity:** Neem derives its chemicals, in particular For its effectiveness as an antibacterial agent, azadirachtin is well known. A complex tetranorteiterpenoid limonoid found in both the seeds and leaves is largely to blame for the plant's harmful effects on microorganisms. Including M. tuberculosis and strains resistant to streptomycin, extracts of the leaves, seeds, and bark have a broad spectrum of antibacterial action against Gram-negative and Gram-positive germs. It blocks M. tuberculosis, Vibrio cholerae, Klebsiella pneumoniae, and M. pyogenes in vitro. Streptococcus mutans and S. faecalis have both been shown to be resistant to the antimicrobial properties of neem extract. Other ingredients that contribute to neem's anti-bacterial activity include nimbidin, nimbin, nimbolide, gedunin, mahmoodin, margolone, and cyclic trisulfide in addition to azadirachtin. Additionally, neem extracts offer a glimmer of hope for the treatment of fatal disorders like Chagas disease in Latin America, which was resistant to all other forms of medication. The parasite that causes this illness is spread by the kissing bug, an insect. According to research, feeding the bugs neem not only rids them of parasites but also stops the adults from reproducing and the young insects from moulting.
10. **Antiviral activity:** aqueous leaf extract offers antiviral activity against Vaccinia virus, Chikungunya and measles virus. Nimbin and nimbidin have been found to have antiviral activity. They affect potato virus X, vaccinia virus, and fowl pox virus.
11. **Anticancer activity**: A research of chemoprotective neem chemicals, such as azadirachtin, nimbolide, and limonoid enhance extracts on models of buccal carcinogenesis in hamsters, found that neem leaf aqueous extract efficiently suppresses oral squamous cell cancer caused by 7, 12-dimethylbenz[a] anthracene (DMBA). Overall investigations showed a reduction in antigen expression and cell proliferation. Additionally, limonoid-derived chemicals from neem have demonstrated strong anti-cancerous effects, according to researchers. These include 15-O-deacetylnimbolindin-B and 1-O-deacetylohchinolide B, both of which have been shown to be effective in preventing cell proliferation in human cervical cancer. Azadiramide-A, an alkaloid-derived limonoid that is largely present in ethanolic extracts of Neem leaves, has been shown in a recent study to inhibit cell proliferation and trigger apoptosis in human breast cancer cell lines MDAMB-231 and MCF-7.
12. **Antioxidant activity:** Neem seed extract has been shown to have antioxidant properties in vivo during the germination of horse grain, which is characterised by low levels of lipid peroxides and lipooxygenase activity. Additionally, a powerful plant lipooxygenase inhibitor known as an antioxidant principle has been discovered. Natural extracts like those from Neem, in forms like teas and oils, seem to be an easy and affordable method to

introduce antioxidants. Neem-derived antioxidants are a simple and cost-effective approach to supplement.

13. **Anti-diabetic effect:** Diabetes is one of the major chronic degenerative disorders now the world is facing. Keeping in view of the severity of disease searching the ways for lower cost treatments must be need of hour.
14. **Effect on central nervous system:** The leaf extract was found to have varying degrees of central nervous system (CNS) depressing action in mice. Significant CNS depressing activity was reported in leaf fractions of acetone extract. In rats, leaf extract up to a dose of 200 mg/kg body weight significantly reduces anxiety. The stem bark and root bark's crude ethanolic extracts displayed hypotensive, spasmolytic, and diuretic properties
15. **Wound healing:** The effects of several plants and their compounds on wound healing are significant. A study was conducted using excision and incision wound models in Sprague Dawley rats to assess the wound healing activity of extracts from the leaves of A. indica and T. cordifolia. The results showed that extracts from both plants significantly promoted the wound healing activity in both excision and incision wound models.
16. **Role in dentistry:** An analysis of neem-based mouthwash's antigingivitis effectiveness revealed that chlorhexidine and A. indica mouthwash are both equally efficient at lowering periodontal indices.
17. **Neem oil:** Neem oil, which is extracted from neem seeds, has a multitude of medicinal characteristics, making it a fantastic additive in cosmetics and other high-quality products like hand soap, cleanser, hair oil, and others. It is recognised to be an excellent mosquito repellent and can treat a wide range of skin diseases. Neem can be combined with coconut oil and applied to the body as well. It is believed that neem oil is promoted to children in India as a sort of cure-all. Neem oil is not only a fantastic Ayurvedic healer, but it can also be used to protect various plants. It can also be found in lotions, cleansers, and other healing products.
18. **Neem cake:** Neem cake is adaptable and has several applications. It might very well be used as normal insecticide, compost, and animal feed. When combined with urea before being applied to the fields, it provides natural nitrogen while also impeding the nitrification process. The use of neem-coated urea in a 90:10 ratio can prevent up to 30% of the harvests total synthetic nitrogen requirement from being wasted. This results in lower production costs for horticulture. In India, neem cake is typically used as compost for sugarcane, vegetables, and other cash crops.
19. **Other uses:** The gum from bark is a stimulant and demulcent tonic, which is another activity. It has immenagogue, antispirochaetal, and anti-leprosy properties. Fever is commonly treated with neem. The ability to reduce fever is anti-pyretic. In addition to

these advantages, neem products also have analgesic (pain-relieving) and anti-inflammatory effects; thus, they can provide organic, affordable, readily accessible, and local medicines for most common illnesses, thereby enabling many people, particularly in rural and tribal areas, to live sustainably.

Conclusion:

Neem is one the best nontoxic biological sources for development of modem drugs. Therefore, wide variety of neem extracts extend their benefits beyond traditional medical folklore, hence through the use of scientific and technological advance now we can use neem extracts as current medical adjuvants, on humans, animals and plants by understanding their potential. Considering the immense importance of this "Kalpavriksha" it can be explored for economic and therapeutic utilization for a sustainable development.

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OBESITY: A PRIORITY CONCERN FOR WOMEN'S HEALTH AND DEVELOPMENT

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Abstract:

Over the last decade, obesity has become a severe health issue among women, accounting to 15% of obese women worldwide. As a result, the epidemic of non-communicable diseases (NCDs) among women has witnessed a steep rise. In low and middle income countries, obesity associated NCDs have become the leading cause of deaths among women, counting to 80% of NCD deaths per year. The modifiable risk factors of obesity are unhealthy diet, physical activity and lifestyle habits like alcohol and tobacco consumption, while non-modifiable factors are genetics and diseases. The increased rate of obesity has severe outcomes on women's overall health and development. Apart from NCDs, the last decade has witnessed higher prevalence of other obesity- induced health issues among women such renal disorders, reproductive diseases and mental health problems, particularly in reproductive and old age. Obese women have been reported to have poor maternal conditions, leading to maternal mortality and poor pregnancy outcomes such as preterm deliveries, nutritional deficiency disorders and developmental anomalies. The overwhelming burden of health concerns associated with obesity pays a heavy toll on medical expenditure and economy in general. It also hampers with the working capacity of women, lowering their productivity and financial stability. Hence, there is a dire necessity to mitigate this epidemic of obesity among women to safeguard their health and economic status. One of the most effective means to eradicate this public health issue is to adopt extensive food-based strategies. Food-based approaches at both household and community levels are sustainable in promoting health of women and population, in general.

Keywords: Obesity, diseases, women, strategies, management

Introduction:

The World Health Organization (WHO) regards obesity as a chronic health condition which has reached epidemic proportions globally, with at least 2.8 million people dying each year as a result of being overweight or obese (Bouayed and Bohn, 2013). In 1995, there were an estimated 200 million obese adults worldwide, while the number of obese adults has increased to over 300 million by the year 2000. Contrary to conventional beliefs, the prevalence of obesity is not restricted to developed counties. The rate of obesity in developing countries is also in the

higher ends, with an estimate of over 115 million. It is predicted that if these secular trends continue, by 2030 an estimated 38% of the world's adult population will be overweight and another 20% will be obese (WHO, 2020).

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. The most widely adopted criteria for classifying obesity is body mass index (BMI; body weight in kilograms, divided by height in meters squared), which ranges from underweight or wasting (<18.5 kg/m^2) to severe or morbid obesity (≥40 kg/m^2). In clinical and research settings, waist circumference, a measure of abdominal adiposity, has also been recognised as an important determinant of overweight/obesity. As per internationally used guidelines, waist circumference ≥90-94 cm in men, and ≥80 cm in women is considered to cause severe metabolic syndromes like obesity, diabetes and chronic cardiovascular disorders. (Arroyo and Mincey, 2016).

The past decade has witnessed a drastic deterioration in women's health status resulting from obesity and related diseases. In 2016, the World Health Organisation (WHO) had estimated that 15% of the world's women population was affected by obesity. They further reported that the since 2016, the prevalence of obesity among women worldwide has been increasing at the rate of 40% each year (Das and Sarma, 2019). Moreover, obesity is considered as both an influencing and resulting factor of the top health issues of women as published by the World Health Organisation (WHO) in 2015, which include cancer, reproductive and maternal health, human immunodeficiency virus (HIV) infection and other sexually transmitted infections, mental health and non-communicable diseases (NCDs). Collectively, obesity induced NCDs have become the leading cause of death for women worldwide. 65% of female deaths across the world are attributed to NCDs, amounting to 18 million deaths each year. This situation is more precarious among women in reproductive age group residing in the developing countries like India. (Chakma and Gupta, 2014). Obesity and its health complications are evident in women from all economic strata. However, global rates of women mortality and morbidity reveal a disproportionate impact of obesity in lower resource settings. Over 80% of obesity associated cardiovascular and diabetes deaths, and almost 90% of deaths from obesity associated chronic obstructive pulmonary disease, occur in low- and middle-income countries. More than two thirds of all cancer deaths occur in low- and middle-income countries, where obesity has been found to be a serious contributing factor. It is very evident that obesity is one of the major concerns in regards to women's health and development (Jastreboff *et al.,* 2019).

There is a huge gender disparity in the causes, consequences and associated disorders of obesity as a result of certain biological, socioeconomic, cultural and gender-related differences (Diplock *et al*., 1998). The consequence of obesity on women's health and development calls for a dire need to prioritize it as a major public health issue. Tackling the rising epidemic of obesity

among women will lead to the assurance of improved health in women and the population as well. This review is an attempt to segregate certain aspects of obesity in women and food-based approaches to tackle the epidemic.

Genesis of obesity in women

Obesity is a resultant of cumulative factors, categorised into modifiable and non-modifiable. The modifiable factors include behavioural problems such unhealthy diet, physical inactivity, alcohol and tobacco abuse. A large percentage of obesity (80-90%) among is preventable through the reduction of these behavioural problems. The rapid onset of urbanisation has transitioned dietary patterns and brought into the practice of increased intake of energy-dense foods which are loaded with saturated fat, sugar and salt. This global nutrition transition has fuelled up rates of overweight and obesity. According to projections given by the WHO it is reported that by the middle of 20th century , an approximate of 1.5 billion adults globally were overweight resulting from unhealthy food pattern, and of those, more than 200 million men and nearly 300 million women were obese (WHO, 2014). Secondly, urbanisation has resulted in fast-paced lifestyle with lower levels of physical activity, increasing the risk of overweight and obesity, diabetes, cardiovascular disease and certain cancers. Evidences from worldwide reveal differences in physical activity levels among the sexes, particularly during the school-going years. Several epidemiological studies have reported that adolescent girls in many low- and middle-income countries have low activity levels and place less value on participating in physical activity (Chooi *et al*., 2019). In several developing countries, physical mobility is often seen to be curtailed by societal and cultural contexts such as "lack of safe and supportive environments, shortage of income and leisure time, negative cultural stereotypes of body image, social norms surrounding dress and mobility or due to the common perception that sport is unfeminine" (Harndy, 2016).

In recent decades, there has been a global increase in the trends of alcohol consumption, occurring majorly in developing countries. Many societal prejudices donot expect women to consume alcohol which in turn, have led to lesser assumption in the alcohol consumption estimates among women. This has resulted in limitations in the early detection and treatment of alcohol-related complications in women. Major government and non-governmental organisations tend to initiate men-oriented alcohol treatment programmes. The situation is exacerbated with increased incidences of health issues associated with alcohol-abuse among women (Martin *et al*., 2015).

In certain medical conditions such as Prader-Willi syndrome and Cushing syndrome obesity is often traced as complication. Arthritis is also found to be associated with obesity as it leads to prolonged reduction in physical activity, which may result in weight gain. Some medications like antidepressants, anti-seizure medications, diabetes medications, antipsychotic

medications, steroids and beta blockers also cause severe weight gain. Obesity is also carried genetically as the gene affects the fat storage and distribution in the body. Genetics may also play a critical role in regulating the body metabolism (WHO, 2015).

Age-related biological factors like menopause, hormonal changes and fat redistribution also lead to abnormal weight gain in women. In most societies, it is observed that health consciousness and awareness is less pronounced in women than men. Women are often seen to be neglecting when it comes to health and nutrition care. In most low economic societies, poor education and economic status causes ignorance among women which exaggerates the prevalence of obesity and its health threats (Warner and Ozanne, 2010). Globally, women account for average 60% of the world's poor. Women's lack of access and control over resources limits their ability to pay for healthcare for. Women in low-income families will often prioritise spending on their family's wellbeing over expenditure on their own health. This situation is aggravated by the higher rates of illiteracy among women than men, which leads to lesser access to health care systems (Berge *et al.*, 2015). Another major risk factor of obesity, particularly among women residing in rural settings is their geographical barrier. Geographical distance dissuades women's accessibility to health education and healthcare as they tend to be less mobile, have lesser chances of owning their own transport and are unable to afford public transport. These constraints are further reinforced by social expectations confining women to remain at home and not travel alone, particularly due to fear of crime, violence and harassment in public or on public transport (Barnes *et al.*, 2015).

Obesity and its affect on women's health

Obesity stands as one of the leading health barriers in women, having a multi-faceted affect in the body's physiology. Obesity is significantly associated with increased mortality, reducing the average life expectancy to 5–10 years. In 2016, a large-scale meta-analysis conducted by the Global BMI Mortality Collaboration has reported that the hazard ratio (HR) for all-cause mortality rose sharply with increasing BMI (Global Mortality Collaboration, 2016).

Obesity is associated with non-communicable diseases (NCDs) as it causes dysfunction of many systems in the body including metabolic, hormonal, hemodynamic, biochemical, immunological and molecular physiology. The phenotypic change in adipose tissues resulting from obesity causes a chronic inflammation, which is characterised by "increased levels of circulating free-fatty acids and pro-inflammatory factors. This chronic inflammation results in vascular dysfunction, including atherosclerosis formation, impaired fibrinolysis and ultimately increasing the risk for cardiovascular diseases. This chronic inflammation is also considered to be a major contributing factor for insulin resistance and type 2 diabetes mellitus.The International Diabetes Federation (IDF) defines central obesity as an essential component of the categorising metabolic syndromes like raised triglycerides, reduced HDL cholesterol, raised

blood pressure, and raised fasting plasma glucose (Barnes *et al*., 2015). Obesity is also linked with the development of certain cancers such as colorectal, pancreatic, kidney, endometrial, breast and oesophageal. Cancer and cancer-associated mortality is reported to be significantly increasing with increased levels of fat and is triggered by the metabolically active nature of excess adipose tissue. Several studies also have focussed on the impact of complex interactions between obesity-related insulin resistance, hyperinsulinemia, sustained hyperglycemia, oxidative stress, inflammation, and the production of adipokines on the formation of cancer (Fruh *et al*., 2013). In many cases, obesity has also been found to be negatively affecting the reproductive health of women. It is linked with reproductive health conditions like anovulation, early puberty, polycystic ovaries, infertility, hyperandrogenism and sexual dysfunction. Obesity is also linked with mental health and is found to be negatively associated with depression, anxiety disorders, neurodegenerative diseases and sleep disorders (Williams *et al*., 2015).

These chronic health conditions and their complications affect the quality of life and life expectancy. Apart from the medical complications, obesity also has certain social and economic barriers. In many cases, obesity hampers with an individual's confidence which, in turn, reduces the ability to face bigger audiences and perform the best. Moreover, in many other cases, the cost and expenditures associated with obesity and its complications has a serious impact on an individual's economic burden (Joshi *et al*., 2014).

Prevention and sustainable management of obesity in women

The rising prevalence of obesity and its consequences needs to be treated with an extensive and sustainable management. It is very well-known that the recent surge in the rates of obesity is driven by dietary pattern and food choices that promote excessive calorie intake. Over the past few years, food industry has been promoting products which do more harm than good to the human body. Several recommendations have been laid down for weight management which mostly emphasize the importance of healthy eating patterns that include a variety of nutrient-dense foods, limit portions of energy-dense foods and reduce overall energy density (Lattimer and Haub, 2010).

Practical strategies for the prevention and management of obesity through dietary approach

1. Balancing energy density: The first step towards management of obesity lies in balancing the energy density in the diet, which is a unifying factor for weight loss. Reducing the diet's energy density allows individuals to consume satisfying amounts of food for fewer calories. Strategies that lower energy density are flexible and can be applied to multiple dietary patterns to match differences in energy needs, taste preferences, eating behaviours, food accessibility and cultural backgrounds (Fall, 2018).

Several research findings show that in order to create a sustainable dietary pattern for weight loss, an individual needs to make changes that balances energy intake while receiving optimal nutrition, thereby controlling hunger and promoting satiety at the same time. One way of balancing energy density is replacing high energy foods with lower energy foods. This can be done by increasing the inclusion of fruits and vegetables in the meals. In order to decrease energy intake in a meal, larger portions of vegetables or fruits must be substituted for foods higher in energy density so that the overall energy density of the meal is lowered. Addition of herbs and spices and including variety are effective ways of making the meal interesting and more palatable, while keeping the meal low in energy but rich in nutritive value (Das and Sarma, 2019).

2. Balancing fat intake: Fat consumption is recommended to be kept in moderation to stay within the recommended energy intakes for weight management. Some methods for moderating fat intake at meals include switching to lower-fat alternatives such as cooking methods which require little or no oil/fat like boiling, grilling, baking etc. Shifts should also be made to decrease the amount of solid fats, which contain saturated and trans fat and to substitute with oils containing polyunsaturated and monounsaturated fats to improve diet quality and overall health. Focus should be on using healthy fats in moderate amounts that improve their diet's palatability (Das and Sarma, 2019).

3. **Including protein and fiber:** Protein and fiber have been known to promote satiety or feelings of fullness. Studies suggest that incorporating more protein can increase satiety and at the same time decreases energy intake. It is encouraged to incorporate recommended amounts of lean protein sources such as chicken breast, legumes or low-fat dairy to create satisfying low-energy-dense meals. Dietary fiber also promotes feelings of fullness by increasing chewing time, promoting stomach expansion and decreasing absorption efficiency. Studies show that increasing fiber at meals can lead to decreased energy intake and increased ratings of fullness. Several evidences prove that diets containing higher amounts of fiber are associated with lower body weights and reduced disease risks. Some randomized controlled trials evaluating the addition of fiber-rich foods, such as legumes, have also found increased fiber to be beneficial for weight management. Fiber is often found in foods low in energy density, such as fruits and vegetables and choosing fiber-rich foods can help enhance satiety, improve overall health and support weight management (Chen *et al*., 2015).

4. Reducing sugar intake: Consumption of foods and beverages containing added sugars is considered as an essential element in the management of obesity. The main sources of added sugars are beverages, snacks, and sweets. Foods such as fruits, vegetables and dairy products contain natural sugars. It is strongly recommended to limit added sugars typically found in nutrient-poor, higher-energy-dense foods and beverages (Chakma and Gupta, 2014).

5. Dietary diversification and its role in the management of obesity: Dietary diversification is an intervention that changes food consumption at the household level. In most low economic societies, starch-based diets with limited access to meats, dairy, fruits or vegetables, are the dominant diets. The objective of dietary diversification is to increase the variety and quantity of nutrient-dense food. This objective is generally achieved through social and behavioural change activities, but can also include increased production of nutrient-rich foods and improved access to diverse foods. It involves changes in food production practices, food selection patterns, and traditional household methods for preparing and processing indigenous foods (Bouayed and Bohn, 2013)

Conclusion:

The rising obesity and its associated co-morbidities in women are creating rippling effects on global health and economic statistics. Women can play a significant role in the fight against obesity, a global epidemic which has been alarmingly increasing among women from both high and low economic countries. The determinants and consequences of obesity must be addressed extensively to women from all societies and equal involvement should be encouraged to create an integrated and sustainable propaganda to curb the issue. The health and well being of women are determinants of a healthier population. It also influences the socio-economic frontline of a nation. This calls for the need to create an elaborative awareness and educational programme for women to fight against obesity effectively. Women play a significant role in determining the food choices and dietary practice in household and community level, in general. Since time immemorial, women are regarded as the most influential element in shaping the dietary habits of a family. Women should be encouraged to utilize the local food resources as an alternative to unhealthier food choices that are available in the market. The practice of kitchen garden and homestead farming should be encouraged to make use of natural food resources, which would be high in nutritive value without any sort of contamination. Nutrition education should an important element in awareness programs, where knowledge on importance of healthy diet and its impact on weight management should be disseminated. Women should be made aware about the nutrition policies and standards that promote effective practices to prevent obesity and other disorders. At the same time, women should be educated on the health hazards of unhealthy lifestyle practices like tobacco and alcohol abuse and promote adequate physical activity in their routine. Women are the future determinants of a healthy nation. Hence, it is the need of the hour to educate the women on the different approaches that can lead to an effective and sustainable management of obesity.

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MALADJUSTMENT OF CHILDREN WITH SIBLINGS OR PARENTS

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In the fast-changing social milieu, the pressure of highly competitive and stressful environment, withdrawing educational and career opportunity, and pressure of peer group creates tremendous social tensions. This adversely affects the personality of adolescents and interfamily relationships between sibling, parents and their children. Stronger relations among families result in stability and externalizing behaviors relating to internalizing behaviors, although children with comorbid disorders experienced the highest levels of family instability (Milan and pinderhughes, 2006).

Parents have certain responsibilities towards their children and they have to exercise these. Parents must recognize this right direct to the children on the right path. At the same time, children have the freedom to chart their own paths within the social norms of society. what is 'Maladjustment' it is a process whereby an individual is not able to satisfy his biological, psychological, or social needs successfully and establishes an imbalance between his personal requirement and expectation of society resulting in the disturbance in psycho-equilibrium. The term maladjustment can be referred as a wide range of social, biological, and psychological conditions.

The word 'maladjustment' is not a medical term indicating a precise diagnosis. It is normally known as a descriptive term for a child 'who is growing in ways that have a bad effect on him or his fellows and cannot be cured by his parents, teachers and other adults in ordinary contact with him.' This is directly connected with the changes they faced during Adolescence. They wish for social approval and social acceptance for self-confidence and safety to get affection and love from parents, teachers, and other members of society. At this stage, adolescents want to stand on their own feet, make their own decisions, plan for their future independently and run their life by themselves. They start to focus on vocational goals and gather them with competition in the field of employment and get frustrated and respond to this situation emotionally and experience some economic insecurity. Their dependence on their friends becomes more important. A situation of having not a single friend is a great threat to them. Now they need and had to follow codes and morals. They have to be sympathetic, unofficial, serving, courteous and respectful. Croppers to learn codes of honesty, observance of low respect to

authorities, codes of sex and so, on may accompany them with great emotional stress. Most adolescents have a fascination for thrill and new experiences. They wanted to do new things and see things for themselves and by themselves. They enjoy exploring new places. By the time children reach the adolescence phase, they had developed a great interest in the opposite sex. Growing up sexually could cause emotional troubles for many young boys and girls. A personal appearance performs an important part in the personality of adolescents. They are very worried about their personal appearance. It influences their personal and social development. Sense of physical inferiority, self-consciousness, shyness, obsession as habits, anxieties about self-control, and many kinds of fears, emotional immaturities, and many other troubles of adolescents may be due to these feelings of lack of personal appearance.

They started expressing their agitations in various forms, like strikes, collective walkouts, buses put to fire, and resorting to so many violent ways. Several forms of rebellion against adult authority has been a normal feature today. The use of alcohal is also linked with other forms of deviancy. Craving for drugs, however, this is a relatively new phenomenon. Having drugs is a result of feeling inadequacy, helplessness, and alienation. They are used as a mode of escape and could direct to depression and paranoid symptoms. Sometimes these changes exercise a big influence on emotional development of adolescents.

Causes of maladjustment

Maladjustment is a multifarious trouble of human behavior no single factor can be pointed as its cause. It is an outcome of multi factors that perform a role in developing personality of the child. There are various factors like- home, society, and school which lead to maladjustment. A big portion of cases of maladjustment comes from unsuccessful families. Their parents may be deceased for divorced and/or working long hours so that they can spend much time with the child. This leads to long-term negligence of children’s wants and needs. As an outcome, they are not enough prepared and thus could barely adjust with their siblings. Constant clashes between parents or other members of the family also make conditions that affect the security, affection, mental stability, and fulfillment of needs of children

Symptoms of maladjustment

The following manifestation may reveal their relationship with other members of the families:

(1) Being disobedient to parents

(2) Staying out late or even absent from home

(3) Siblings' enmity,

(4) Not concerned for the needs of their families.

How to help maladjusted children

Daily life can be exceptionally difficult for a maladjusted child. Children who are maladjusted lack the social skills. It is essential to interact effectively with peers and connect in healthy and cooperative activities. For helping maladjusted children we first have to recognize the reason which could be number of things. For this, speak every day to the child about his day. By engaging in habitual communication, the child starts to learn the principles of socialization. Went to popular parks or other amusement areas in which children generally play. cheer the child to engage in play with his peers.

Some maladjusted children behave badly because they do not know how to behave properly. As parents give an explanation to the child that what she/he did was wrong, so she/he can better understand why she shouldn't repeat this behavior. Understand your children's feelings, even if you don't all time approve their behavior. Avoid humiliating your children and laughing at what may seem to you to be immature or idiotic questions and statements. Help your children build self-confidence by encouraging their participation in activities of their choice (not yours). Support your children to involve in decision-making for the family and to work out family concerns together with you. Understand that your children need to confront your opinions and your traditions of doing things to achieve the disconnection from you that's important for their own adult identity.

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DEVELOPMENT AND EVALUATION OF ORAL BILAYER PUSH-PULL OSMOTIC PUMP FOR SIMULTANEOUS DELIVERY OF LORNOXICAM AND CAPSAICIN

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Abstract:

Controlled drug delivery system offers therapeutic advantage, compliance and efficacy. Osmotic drug delivery system holds a prominent place in controlled drug delivery system which promises a constant and controlled release drug for a prolonged period. Lornoxicam and capsaicin was selected in this formulation as a combined drug therapy for treating patients with Rheumatoid arthritis, and H-Pylori infection co-morbidities. Lornoxicam and capsaicin belongs to class II BCS group, was formulated as Bilayered Push Pull Osmotic Pump (PPOP),using a combination of low and high molecular weight compatible polymer polyox of differing viscosity, molecular weight and osmogen concentrations in push and pull layers; Push Pull Osmotic Pump (PPOP) formulation was coated with cellulose acetone, after making indentation of varying diameter and depth. Granules and the formulated tablet was evaluated for standard Granules, pre-formulated tablets, coated tablets, all passes the test for standard, and parameters lies within the I.P limits.

Keywords: Push Pull Osmotic Pump PPOP, Controlled drug delivery system, Capsaicin, Lornoxicam, Osmotic pump, Multi drug therapy.

Introduction:

Controlled drug delivery systems delivers constant plasma level, which offers therapeutic advantage for drugs in terms of compliance and efficiency. Osmotic drug delivery system holds a prominent place among Modified release systems. Delivery rate at zero order kinetics is achievable which promises a constant dose and release of drug in the biological systems by ODDS. One of such controlled drug delivery system is push pull osmotic drug delivery systems (PPOP), [1,2] and a bilayered tablet with PPOP reveals a promising drug delivery to different class of BCS group and other profile of PPOP and it is independent of drug property and release environment. Osmotic drug delivery system is the drug which may be osmotically active (or) with an osmotically active agent is encapsulated in a insoluble semi permeable membrane[3,4] which needs an orifice on the surface of drug layer after coating made by mechanical drilling[5]. Modified release (MR) dosage forms are developed by altering drug absorption or the site of drug release in order to achieve predetermined clinical objectives. Possible therapeutic benefits of an MR product include improved efficacy and reduced adverse events, increased convenience

and patient compliance, optimized performance a greater selectivity of activity or new indications.

In developing oral products, two types of osmotic pump systems have been utilized. These are a one chamber EOP system and two chamber system (e.g. Push-Pull). In general, an EOP system is only feasible for molecules with a narrow range of solubility (e.g. approximately 50-300 mg/ml) [6] to achieve zero order and complete release. The two-chamber device was designed mainly to accommodate less soluble drug or higher drug loading. It consists of bi layer tablet with one push layer containing a highly swellable polymer and a drug- containing layer. In the GI tract, water is imbibed through semi - permeable membrane into both layers by the osmotic excipients. As both the drug and push layers hydrate, a drug suspension or solution is formed in situ and the push layer begins to expand as a result of the hydration and swelling of the hydrophilic polymers. Drug release begins when the volumetric expansion of the push layer starts to "push" the active in the drug layer through the orifice on the drug layer side. Because rate control resides with in the rate controlling membrane, drug release is essentially insensitive to environmental effects, such as pH, agitation and type of apparatus.

Drug profile: Capsaicin

Capsaicin, a predominant molecule of capsicum species, the chemical moiety presents in capsaicin, representing the degree of pungency being capsaicinoids, a vanilloid pharmacophore which is 3 hydroxy-4-methoxy benzyl amide. Analogs and its isomers of capsaicin are differs in their hydrophobic alkyl side chain and occurrence, where as analogs differs in chemical moiety and occurrence probably gives an output of trans isomer, and rarely cis-isomer. Pharmacological activity is depends upon its aliphatic side chain.

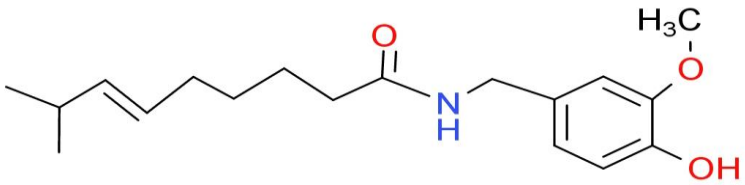
Chemical name: 6-nonenamide, moiety,

(E)-N-{4 hydroxy-3 methoxy-phenyl) methyl}-8 methyl nonenamide;

(E)-8 methyl-N-Vanillyl-6 Nonenamide.

Chemical constituents:[7]

By nature Capsaicin is a highly volatile hydrophobic, colorless, odorless and waxy alkaloid with the molecular weight of 305.41 g/mole. Structurally Capsaicin belongs to a group of chemicals called "Vanilloids" structure consists of three regions. They are a head region with vanillyl group (Methyl catechol), a central region with amide bond, and third region being aliphatic hydrophobic side chain.



C- Region	B- Region	A -Region
Aliphatic Hydrophobic Side chain	Amide bond	Vanillyl group (Methyl catecol)

All capsaicinoids have a similar structure and they vary in the length and degree of saturation of alkyl side chain of aliphatic region (c).

Physico chemical properties:

Description	**Properties**
Chemical formula	$C_{18}H_{27}NO_3$
Molecular weight	305.41 g/mole
Melting point	62-65^oC
Boiling point	210-220^oC
Flash point	113^oC
Solubility	In water 28.93mg/L at 25^oC, freely soluble in alcohol, ether and benzene.
UV-VIS (max)	280 nm
Vapour pressure	$1.38*10^{-8}$ mm Hg at 25^oC

Pungency[8]:

The "Pungency" of capsaicin as predominant component including other Capsaicinoids of chilli pepper and Spicy foods, was measured in terms of "Scoville scale", which is recorded in scoville heat units (SHU). Scoville heat units: SHU Indicates how "spicy" (pungency or hotness) a pepper is, which depends on its quantity of capsaicinoids per unit weight of the chilli. Pure Capsaicin shows a high score of 16,000,000 pioneering in "pungency" and it is due to the presence of vanillyl moiety.

Capsaicin plays various therapeutic roles.[9,10,11] Helicobacter pylori known as Campylobacter pylori are a gram (-) ive microaerophilic bacterium found in the stomach. Time dependent and concentration related studies of capsaicin gastro protective effect against H. Pylori induced gastritis and duodenal diseases reveals capsaicin specifically inhibited the growth of H. Pylori dose dependently at concentrations greater than 10micro gram/ml. Capsaicin continued to exhibit bactericidal activity as low as pH 5.4 for 4 hours. Researcher suggests that capsaicin stimulates Mucus output, and might involve luminal dilution through increased gastric fluid volume. In addition, it is noticeable that high concentration of capsaicin may induce an initial protective effect, with signs of desensitization appear at later time capsaicin use as cytoprotectants, related to the prostaglandins has invited the attention of many investigators[12,13,].

Pharmacokinetic parameter

Absorption: Nearly 94%of orally administered capsaicin was absorbed and maximum concentration in the blood was reached 1 Hr after administration.

Plasma half life: 4.61±0.44 Hrs

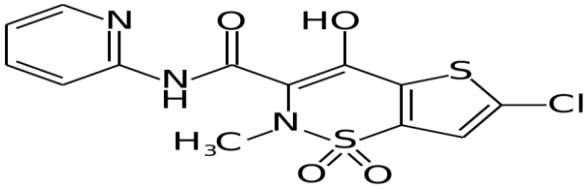
Elimination half life: The elimination half life capsaicin in the plasma was found to be 1.34 Hrs

Bio availability: 50 – 90 % orally

Metabolism: capsaicin metabolized by microsomal cytochrome p450 – dependent mono oxygenase in the liver.

Drug profile: Lornoxicam[14,15,16,17]

Lornoxicam is widely used in management of pain associated with Rheumatoid and osteoarthritis. LORNOXICAM is an Class II BCS (Bio Pharmaceutical Classification System) extremely potent member of the Oxicam group of non steroidal anti- inflammatory drugs (NSAIDs) , with shorter half life (3 –4 Hrs), makes the development of modified release dosage form extremely advantageous, Non selective NSAIDs that inhibition of prostaglandin synthesis by inhibition of(both COX I & II). Lornoxicam PPOP formulation to minimize the GIT disturbances such as peptic ulceration



IUPAC name: (3E)-6-chloro-3-[hydroxyl (pyridine-2-ylamino) methylene]-2-methyl-2, 3-dihydro-4H-thieno [2, 3-e][1,2]thiazin-4-one 1,1-dioxide

Description	**Properties**
Chemical formula	$C_{13}H_{10}CLN_3O_4S_2$
Molecular weight	371.8192 g/mole
Melting point	225-230^oC
Solubility	Poorly soluble in water, Soluble in 0.1N NAOH solution. DMSO:5mg/ml. hardly soluble in water
UV-VIS (λmax)	380 nm
Colour	yellow crystalline powder

Pharmacokinetic properties:

Absorption: completely absorbed after oral administration, reaching plasma concentration within 1-2 hrs

Plasma half life: 3 - 5 hrs

Elimination half life: 3 - 4 Hrs (Aprox. 2/3 is eliminated via the liver 1/3 via the kidney)

Bio availability: 90 - 100% (I.V), 90 % (oral)

Metabolism: Extensively metabolized in liver (5- hydroxylation)

Dose: Oral in a daily dose of 16 mg in two (or) three divided doses.

Drug selection of compatible combination for comorbidity: [18, 19]

Arthritis a disorder with severe inflammatory response necessitates the use of NSAIDs, Patients with colonization Gastric pathogen H.pylori, prone to develop gastric ulcer. Patient getting treatment for Arthritis and with comorbidity of H.Pylori infection, have supra exposure of NSAID induced and gastric pathogen induced ulcer with high risk and proves fatal.

In this study, Lornoxicam and capsaicin was selected as a practically insoluble model drug, Furthermore, the developed osmotic system approach to investigate of combination drug therapy with Lornoxicam and Capsaicin as bilayer tablet offers versatility in treating patient with arthritis and with comorbidity of H.Pylori infection.

Experimental

1. Materials:

Lornoxicam was obtained as a gift sample from Purechem laboratories. PEO (Low and High Molecular weight) gift sample from Lyrus life sciences Pvt. Ltd.,Cellulose Acetate NF gift sample from Mylan Laboratories limited,PVP K-30 gift sample from AVI Technologies. All other chemicals and reagents used were of AR grade.

2. Pre formulation:

By Infrared Spectroscopy[20]

This Preformulation study includes drug polymer compatibility study and analytical investigation of drug. The infra red spectra of Pure Lornoxicam and Capsaicin were recorded by Shimadzu IR spectrometer. Spectrum was measured over a frequency range of 4000-500 cm^{-1}.the peaks obtained in the spectra were compared with corresponding functional groups in the structures of Lornoxicam and capsaicin.

UV Spectroscopy analytical investigation [21, 22, 23]

By UV Spectroscopy analysis of Lornoxicam and Capsaicin. The absorbance maxima have been specified is determined by using UV. From the U.V analysis, it was concluded that the Lornoxicam had shown λ_{max} at 380 nm and capsaicin λ_{max} at 281 nm. Therefore, the observed λ_{max} of Lornoxicam 376 nm and capsaicin 281 nm has selected for further experimental work in pH 6.8 Phosphate buffer and pH 1.2 HCL buffer respectively.

Effect of Formulation and Processing Variables on Performance of the Osmotic Table

Various formulation factors and parameters were examined to identify potential critical factors affecting the bilayer tablet cores and hence the performance of the resulting osmotic tablets.[24,25] The formula and design of experiment has been reviewed by Lyrus Life sciences Pvt, Ltd. Given in Table1.

Table 1: Formula design received from Lyrus Life Sciences

Sr. No.	Factors	Low (%)	Optimum (%)	High (%)
1	POLYOX, High molecular weight (in push layer)	3	5	7
2	POLYOX, Low molecular weight (in pull layer)	3	5	7
	Total	6	10	14
3	SODIUM CHLORIDE (in push layer)	5	10	15
4	SODIUM CHLORIDE (in pull layer)	5	10	15
	Total	10	20	30

Based on review the composition and the technology for the process shown in Table.1. Critical factors were identified for optimization, below mentioned are the critical factors that can be affect drug product performance. The bilayer tablets were tested for in vitro drug release, further investigation of the significance of every variation in formulation or processing conditions, the drug release profiles of the resulting tablets were compared and tabulated.

The modifications in formulation or processing conditions based on optimization factor in table 1 was presented in Table 2

Table 2: Modifications in formulation or processing conditions

Pull Layer	Polymer (low Molecular weight)	Osmogen
Low	3%	5%
Optimum	5%	10%
High	7%	15%
Push Layer	Polymer (High Molecular weight)	Osmogen
Low	3%	5%
Optimum	5%	10%
High	7%	15%
Low-High	3%	15%
High-Low	7%	5%

Evaluation of Formulation Factors:

Effect of various grades of POLYOX in Pull and Push layers: [26]

To evaluate the effect of molecular weight of the polymer, various grades of POLYOX, i.e., WSR N-80 NF, Coagulant NF, or 303 NF for the individual grades of POLYOX were incorporated within the pull- and push-layer formulations at the same levels were investigated.

Effect of osmogen quantity in Push layer:

Sodium chloride was used at varying levels of 3, 5, 7% w/w within the pull and push-layer formulation. As the level of salt was increased, the level of polymer (POLYOX Coagulant) was decreased accordingly.

Effect of osmogen location:

The effect of Nacl location was evaluated in pull and push layer and in both pull and push layers (optimized proportion respectively).

Incorporation of NaCl in the pull and push layer was achieved by varying the level of POLYOX N-80 in the formulation.

Formulation of bilayer indented PPOP tablet (two chamber system)

Preparation of pull and push layer granules the composition is given in table 3a, 3b, and 3c.

PULL LAYER (320mg)	INGREDIENTS	A					
		POLY ETHYLENE OXIDE (PEO) – 3% (LOW MOLECULAR WEIGHT)					
		SODIUM CHLORIDE (Nacl) – 5%					
	CAPSAICIN	50µg					
	PEO (LOW) (mg)	9.6					
	LACTOSE (mg)	276.75					
	PVP-K30 (mg)	6.4					
	NaCl (mg)	16					
	TALC (mg)	8					
	MAGNESIUM STEARATE (mg)	3.2					
PUSH LAYER (160mg)	INGREDIENTS	PEO (High molecular weight)	A1	A2	A3	A4	A5
			3%	5%	7%	3%	7%
		Nacl	5%	10%	15%	15%	5%
	LORNOXICAM (mg)		8	8	8	8	8
	PEO (HIGH) (mg)		4.8	8	11.2	4.8	11.2
	LACTOSE (mg)		130	118.8	107.6	114	123.6
	PVP – K30 (mg)		4	4	4	4	4
	Nacl (mg)		8	16	24	24	8
	TALC (mg)		3.2	3.2	3.2	3.2	3.2
	MAGNESIUM STEARATE (mg)		2	2	2	2	2

PULL LAYER (320mg)	INGREDIENTS	B
		POLY ETHYLENE OXIDE (PEO) – 5% (LOW MOLECULAR WEIGHT)
		SODIUM CHLORIDE (Nacl) – 10%
	CAPSAICIN	50µg
	PEO (LOW) (mg)	16
	LACTOSE (mg)	254.35
	PVP-K30 (mg)	6.4
	NaCl (mg)	32
	TALC (mg)	8
	MAGNESIUM STEARATE (mg)	3.2

PUSH LAYER (160mg)	INGREDIENTS	PEO (High molecular weight)	B1	B2	B3	B4	B5
			3%	5%	7%	3%	7%
		Nacl	5%	10%	15%	15%	5%
	LORNOXICAM (mg)		8	8	8	8	8
	PEO (HIGH) (mg)		4.8	8	11.2	4.8	11.2
	LACTOSE (mg)		130	118.8	107.6	114	123.6
	PVP – K30 (mg)		4	4	4	4	4
	NaCl (mg)		8	16	24	24	8
	TALC (mg)		3.2	3.2	3.2	3.2	3.2
	MAGNESIUM STEARATE (mg)		2	2	2	2	2

PULL LAYER (320mg)	INGREDIENTS	C					
		POLY ETHYLENE OXIDE (PEO) – 7% (LOW MOLECULAR WEIGHT)					
		SODIUM CHLORIDE (Nacl) – 15%					
	CAPSAICIN	50µg					
	PEO (LOW) (mg)	22.4					
	LACTOSE (mg)	231.95					
	PVP-K30 (mg)	6.4					
	NaCl (mg)	48					
	TALC (mg)	8					
	MAGNESIUM STEARATE (mg)	3.2					
PUSH LAYER (160mg)	INGREDIENTS	PEO (High molecular weight)	C1	C2	C3	C4	C5
			3%	5%	7%	3%	7%
		Nacl	5%	10%	15%	15%	5%
	LORNOXICAM (mg)		8	8	8	8	8
	PEO (HIGH) (mg)		4.8	8	11.2	4.8	11.2
	LACTOSE (mg)		130	118.8	107.6	114	123.6
	PVP – K30 (mg)		4	4	4	4	4
	NaCl (mg)		8	16	24	24	8
	TALC (mg)		3.2	3.2	3.2	3.2	3.2
	MAGNESIUM STEARATE (mg)		2	2	2	2	2

Table 3 (a, b, c Total: Pull layer * Push layer (3 * 5 = 15) Formula to be optimize.)

Granulation and tablet compression: (two chamber system)[27,28,29,30]

Drug layer granules: Pull layer ingredients, Capsaicin 50 microgram, along with the Low molecular weight polyethylene oxide polymer and sodium chloride osmogen was mixed separately using acetone as solvent, the acetone was added to drug layer ingredients form a damp

mass and passed through sieve No.10, and dried at room temperature to cease acetone followed by drying at hot air oven at 40^0 c for 30 min; Dried granules was passed separately through a sieve number #25(Pull layer) to get uniform particle size. Prepared granules then lubricated with

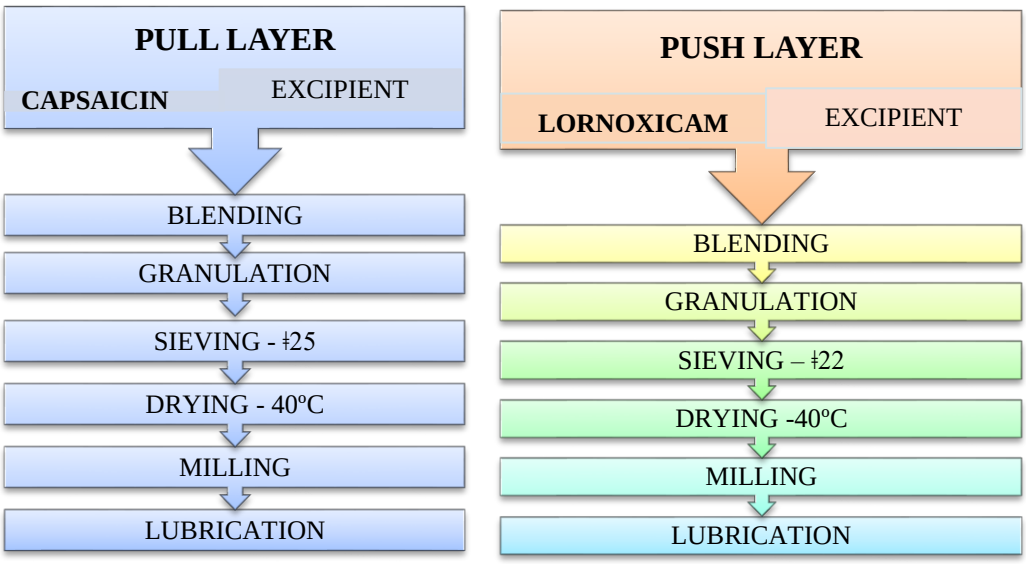
Push layer granules: Blend separately the LORNOXICAM 8 mg, high molecular weight polyethylene oxide and sodium chloride which were sieved through sieve No.10, mixed separately acetone as solvent, and dried at room temperature to cease acetone followed by drying at hot air oven at 40^0 c for 30 min; Dried granules was passed separately through a sieve number #22 (Push layer) to get uniform particle size. Prepared granules then lubricated with talc and magnesium sterate, and mixed well.

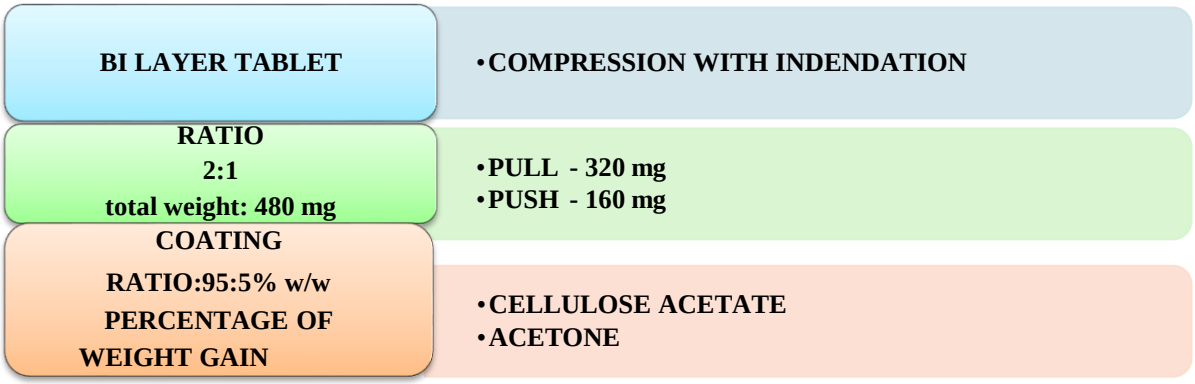
Tableting: Fill the 320 mg in pull layer with capsaicin the dose of 50µg, 160 mg in push layer with Lornoxicam the dose of 8mg and it has Lornoxicam yellow coloured granules differentiated by coloured was first placed in die cavity followed by pull layer granules into the die of the tableting machine, using a Multi rotary tablet machine by double compression method, with 11mm modified concave punches. Modified detachable upper punch contains needle in the convex surface(Mechanical drilling), to make indentation depth of 1.5mm and the diameter of the needle was optimize to produce pore size in the range of (0.6-1.0mm) on the tablet core.and then pressed it by appropriate pressure. Finally, the entire core of the compressed indented bilayered tablet was finished. The two layered osmotic pump tablet is achieved by coating the indented tablet. The weight of each tablet is maintained within the range of 480 to 520 mg. Hardness of the core tablets were with 5-7kg/$cm^{2.}$ The drilled tablets are coated. Shown in Figure.1a

Total 15 formulation codes and the composition shown in Table-3a, 3b &3c

Formulations of core push pull osmotic tablet:

Figure.1a

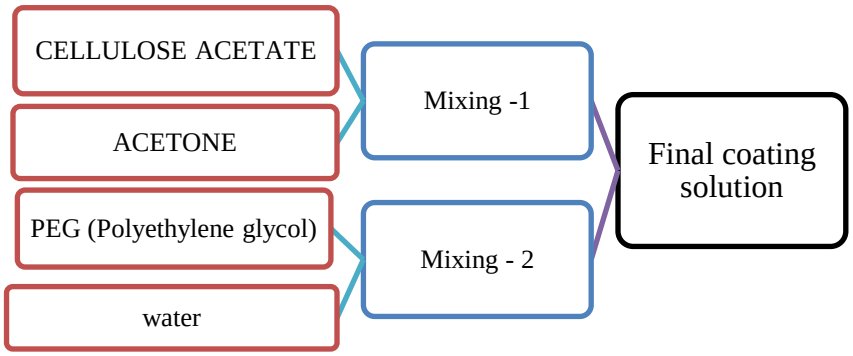




Coating: The indented bilayered core tablet was coated with acetone solution (ratio: 95:5% w/w percentage of weight gain %) of 15 gm Cellulose acetate. The coated product was dried at 40 c for 12 hours. Shown in Figure.1b

Preparation of coating solution: Method of coating solution preparation and optimized parameters used in coating process:

Figure.1b



Step: 1 Cellulose acetate was dissolved separately in acetone.

Step: 2 PEG was dissolved in water.

Followed, in addition of aqueous PEG (mixing 1) solution into the organic cellulose acetate (mixing 2) solution. Then the final coating solution was mixed for 60 – 90 minutes at 500 rpm by using mechanical stirrer which is used for film coating process.

Pan coating process:

The conventional coating pan used for the film coating process. In this method the tablets are placed in a rotating pan and the coating solution were sprayed on the tablets, followed by drying which is used to remove the solvent. Finally a thin film formed around the each tablet. Shown in Table.4

Parameter	**Range**
Gun to bed distance	30 – 45cm
Inlet temperature	41 – 43^{o}C

Exhaust temperature		30 – 33^{O}C
Air flow		Medium
Approximate coating time		90 minutes for 200 ml
Fluid delivery rate		1.5 -2.5 ml per minute
Pan speed	Slow	35 rpm
	High	50 rpm

Evaluation:

a. Pre-compression Characteristics: The following parameters are determined.

Angle of Repose:

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured, and the angle of repose was calculated using the following equation: [4, 5]

$\tan \theta = h / r$

Where, h and r are the height and radius of the powder cone respectively.

Bulk Density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break and agglomerates formed was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its weight onto a hard surface from the height of 2.5 cm at 2-sec intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas: [4, 5]

LBD = Weight of the powder / Volume of packing

TBD = Weight of the powder / Tapped volume of packing

Compressibility Index:

The compressibility index of the granules was determined by Carr's compressibility index [31, 32]

Carr's index (%) = (TBD – LBD) x 100 / TBD

Hausner's Ratio:

The Hausner's ratio is a number that is correlated to the Flowability of a powder or granular material[4, 5]

Hausner's ratio = TD / BD

b. Post-compression Characteristics:

Size and shape:

Standard concave- 11mm- (Fill volume: 480mg-520mg for uncoated tablet; weight gain after coating 540mg-560mg) is measured by using a micrometer and sliding Caliper scale is used to measure the size of 5 to 10 at a time. In laboratory scale tablet size measured by the Vanier caliper. Tablet thickness should be controlled within ± 5% variation of a standard value [6].

Hardness:

Tablet hardness and strength are essential to see that the tablet can shock and stress during manufacturing and coating process, for each formulation, the hardness of tablet determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg.

Thickness:

The thickness of the uncoated and coated tablets were measured using vernier caliper

Organoleptic Characters of Tablet:

General appearance would include some aspects like size, shape, odor, taste, texture, legibility and identifying indentation marks of the tablet is noted after coating.

Friability:

Twenty tablets were rotated in a friabilator (Roche) at 25 rpm for 4 min. the tablets were then dedusted, and the loss in weight due to fracture or abrasion was recorded as percentage weight loss (%friability)[6].

Friability (%) = Initial Weight – Final weight/ Initial Weight

Weight variation test and percentage weight increase:

Twenty tablets were selected randomly from coated and uncoated tablets, average weight and individual weight of both the formulations was noted. Difference in average weight and individual weight should not be more than ± 5% and the difference between weight variation lists was done to confirm, the weight uniformity of prepared formulation and to differentiate the percentage weight gain of coated and uncoated tablets.

Difference in coated and uncoated tablets shows the percentage of weight gain. Prepared tablets pass the limits of I.P. in weight variation.

Percentage of weight gain was calculated by noticing difference in weight of coated and uncoated tablet.

Drug content:

Tablets from each formulation were weighed and, then crushed in a mortar. The drug weight equivalent to 8 mg Lornoxicam and capsaicin 50 µg was taken, and dilution was prepared

to form concentration up to range 10 ppm concentration. Finally, the absorbance of the prepared solution was checked and compared with theoretical value.

***In-vitro* Drug Release Study:**[33,34,35]

The *in-vitro* dissolution study of formulated Lornoxicam and capsaicin tablets were carried out using USP apparatus Type-II in 500 ml of Acid/phosphate buffer solution (pH:1.2/ 6.8) at 37^0C $\pm$0.5 ^{0}C at a rotational speed 50 rpm. The 5 ml sample of dissolution medium was withdrawn and it was replaced by fresh dissolution media to maintain sink condition. Collected samples analyzed spectrophotometrically at 380 nm by using Shimadzu-1700 UV / visible spectrophotometer. The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally[6].

Percentage of drug release of capsaicin was validated by HPLC method. Parameter of HPLC used for validation was presented in Table.5

The amount of capsaicin released from PPOP at each time point was measured using a validated high performance liquid chromatography (HPLC) method.

Parameter	**Condition**
Mobile phase	Orthophosphoricacid,Acetonitrile,water
Wavelength	281 nm
Stationary phase	C18 Column (100*4.6mm,5µ
Flow rate	1 ml
Pump pressure	100
Injection volume	50 µl
Run time	7.5 minute
Pump mode	Isocratic

Disolution parameters:

Method	:	USP II Paddle Method.
Rotation Speed	:	50rpm
Dissolution Medium	:	Acid 0.1N HCL
		(For 2 Hours pH 1.2 after Phosphate Buffer pH6.8)
Volume	:	500 ml
Reference standard	:	Lornoxicam 8.0mg
Temperature	:	37 + (0.5 c)
Sampling intervals	:	First 3 readings every hour after every 2 hours.
No. of tablets	:	6 tablets of each test.

Scanning Electron Microscopy (SEM):[36.]

The coating membranes (before and after dissolution studies) were examined for their porous morphology and for the measurement of orifice diameter using Scanning Electron

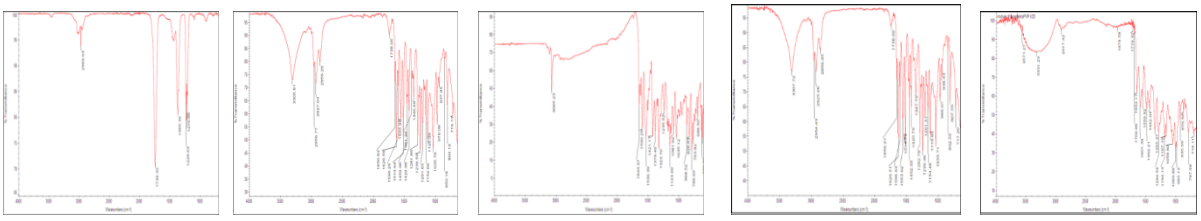
Microscopy (SEM). The samples were placed on 12mm spherical brass stubs with a double backed adhesive tape. The mounted samples were sputter coated for 5-10min with platinum using fine coat ion sputter and examined under SEM.

Results and Discussion:

By Infrared Spectroscopy:

Spectrum was measured over a frequency range of 4000-500 cm^{-1}.The peaks obtained in the spectra were then compared with corresponding functional groups in the structures of Lornoxicam and capsaicin.Peak heights of functional group shows there is no interation between drug and polymer. Figure.2

Capsaicin Capsaicin + Polymer Lornoxicam Lornoxicam + Ploymer Mixture core tablet



UV spectrum analysis of Lornoxicam and capsaicin:

Estimation of Lornoxicam and capsaicin was carried out by SHIMADZU-1700 UV spectrophotometer. Lornoxicam showed maximum absorption 381 nm and 281 nm for Capsaicin in 0.1N HCL (pH1.2) and phosphate buffer (pH6.8). Standard calibration curve obeyed Beer's Law at given concentration range of 5 ug to 100 ug. The value of regression coefficient was found to be 0.999 for Lornoxicam and 0.998 for capsaicin, which showed linear relationship between concentration and absorbance. The results shown in Figure.3a, b.

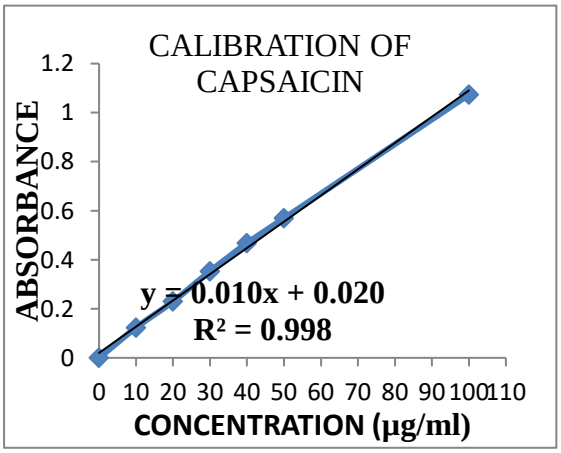


Figure.3a

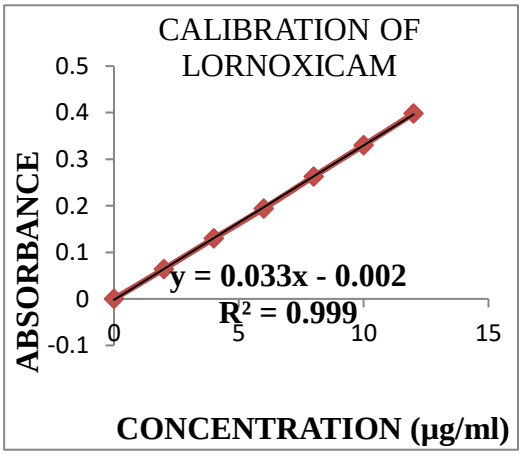


Figure.3b

Calibration of Capsaicin

100mg of Capsaicin was dissolved in 100 ml of methanol (Stock A).From this 10ml was taken and was made upto 100 ml of Methanol (stock B).

From this stock solution (100µg/ml), a series of concentrations 10, 20, 30, 40, 50,100 µg/ml were prepared and the samples were scanned using UV- spectrophotometer. The

maximum wavelength was found to be at 281 nm. The absorbance was noted at 281nm using UV spectrophotometer and the graph were plotted with concentration on X axis and absorbance on Y axis.

Calibration of Lornoxicam

100mg of Lornoxicam was dissolved in 10 ml of methanol and made up to the volume with Ph 6.8 phosphate buffer. From this 10ml was taken and was made up to 100 ml of Ph 6.8 phosphate buffer.

From this stock solution (100µg/ml), a series of concentrations 2, 4, 6, 8, 10, 12 µg/ml were prepared and the samples were scanned using UV- spectrophotometer. The maximum wavelength was found to be at 380 nm. The absorbance was noted at 380nm using UV spectrophotometer and the graph were plotted with concentration on X axis and absorbance on Y axis.

Evaluation of Granules/Uncoated and coated Tablets

a. Pre compressional parameters for Granules:

Powder blends of all the formulations were evaluated for bulk density, tapped bulk density, angle of repose and Carr's index in flow/ compressibility index. Optimised and selected C5 formulation Shown in table 5

Table 6

Formulation C5	**Pull layer : C PEO-7% (Low Molecular Weight) Nacl-15%**	**Push layer : 5 PEO-7% (High Molecular Weight) Nacl-5%**	**Micromertic Properties**
Bulk Density (G/Cc)	0.3886	0.3759	
Tapped Density(G/Cc)	0.5555	0.4840	
Carr's Index (%) Compressibility	30.04%	22.33%	Suitable for direct compression into bilayered tablet
Hausners Ratio	1.4294	1.2875	
Angle of Repose (Degree)	40	35.53	This indicates good flow properties of powder.

b. Post compressional parameters for Granules:

The uncoated tablets were biconvex, bilayered circular shape tablet with pink on push layer and white on drug layer with indentation. The tablets were tested for hardness, thickness, friability, weight variation, percentage of drug content

Table 7

Evalution Parameters	**C5**	
	Uncoated	**Coated**
Hardness((kg/cm²)	5.1	11.0
Membrane Thickness(mm)	4.70	5.20
Weight variation %	490	540
Friability of tablets %	0.36	0.02
Drug content % Capsaicin Lornoxicam	- 	 101.20% 104.20%

The coated tablets were off white in colour, circular and biconvex in shape. They were glossy and elegant in appearance. Parameters percentage of weight increase, coated tablet drug content analysis. All the values given in table6. All the values were found to be within the IP limits (±5%).

In-vitro dissolution studies:

In vitro release study was performed in a USP Dissolution Apparatus Type II using the paddle method. The dissolution media used is Hydrochloric acid buffer pH 1.2 (500 ml) was used for first 2 hrs and Phosphate buffer pH 7.4 (500 ml) for subsequent 10 hours; the results were shown in Table.8b by measuring the absorbance of the samples at 380 nm using UV-Visible Spectrophotometer. Dissolution studies was carried out for capsaicin release from PPOP for the first shows and drug content was validated by for best HPLC and percentage of drug release was presented in Table.8a.

Table 8a: Capsaicin HPLC release for C5 formulation (Best out of 15 formulation)

TIME in Hours	**% CONTENT**	**% of Drug release**
1	**0.0278**	**55.57**
2	**0.0502**	**101.20**

Table 8b: UV visible spectrophotometer absorbance for C5 formulation (Best out of 15 formulation)

Time in Hours	**% Content**	**% of Drug release**
1	**4.72**	**59.06**
2	**4.92**	**61.49**
3	**4.13**	**51.63**
5	**4.24**	**53.01**
7	**4.35**	**54.39**
9	**6.37**	**79.62**
12	**7.81**	**97.68**

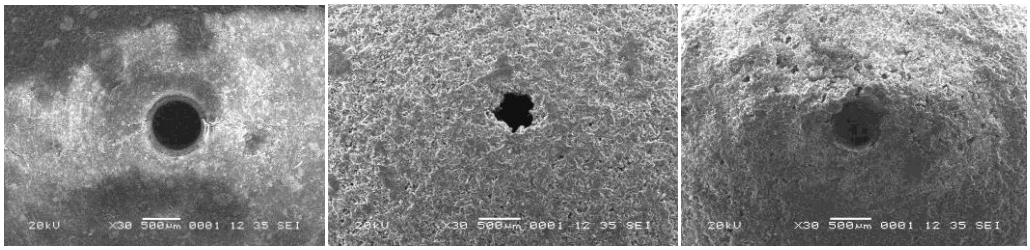
Release of Lornoxicam by in vitro studies was carried out by continuing the studies for 10 hours after replacing the dissolution media by phosphate buffer pH 7.4. Percentage of drug release of Lornoxicam from PPOP has been presented in Table.8b by spectrophotometric estimation 380nm.

Scanning electron microscopy (SEM):

The SEM studies were conducted to elucidate the changes in the membarane structure and orifice diameter before coating, after coating and after in-vitro dissolution studies. It was found that there was no significant difference in the membarane structure and orifice diameter before coating and after dissolution.the results are shown in the Figure.4

Figure 4

Before coating **After coating** **After dissolution**



Summary and Conclusion:

Lornoxicam and capsaicin, as bilayered PPOP formulation after compatible and controlled release drug delivery.

Selected polymer was compatible, and differing molecular weight offers, osmogenic effect with Nacl in push layer and effective release in pull layer.

Osmotic drug delivery system requires indentation, to relax the drug, which was done with modified upper punch with needle.

FTIR studies with peak of the same heights confirm the compatibility of drug and polymer.

Scanning electron microscopy confirms the membrane structure and orifice before and after coating.

Prepared granules, tablets before and after coating passes the tests for standard and confirms within I.P limits.

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ANTIMICROBIAL PROPERTIES OF SELENIUM NANOPARTICLES ON FEMALE RELATED DISEASES

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Introduction:

According to ASTM standards, the particles which are having two or three of their dimensions in the nanoscale (ranging from 1nm to 100nm) are termed nanoparticles [1, 2]. Their importance in different fields like drug delivery medicine, drug delivery, biosensors, cosmetics, paints, and electronics has increased [1, 2, 3]. Due to this, researches in nanotechnology have risen rapidly. Their distinctive properties like small size with a particular shape, large surface area to volume ratio, chemical composition, crystallinity, electronic property, solubility, functional groups, etc have enhanced their efficiency. Because of its distinctive physicochemical properties, it is capable of causing adverse effects on organs, tissues, cells, subcellular organelles, and DNA. So, its toxicity level is always analyzed. These nanoparticles can be synthesized by physical, chemical, and biological methods. Each method is found to have its own advantages and disadvantages. So, the synthesis is being done according to the application and requirement.

The word selenium came from the Greek word 'Selene' which stands for their moon [4] goddess. It was discovered in 1818 by Jons Jacob Berzelius. In the periodic table, it belongs to the 16th group. It is a naturally occurring metalloid element that is commonly found in all-natural materials such as rocks, soils, water, air, plant, and animal tissues. It is an important trace microelement that is necessary for the growth and development of living organisms. It is a vital element in biological bodies and has vast significance in nutrition and medicine. It has a narrow range for the supply, i.e., between 400 µg and 40 µg/day. The 400µg/day shows the toxic level, while the 40 µg/day shows the dietary deficiency level [5].The toxicity of selenium (selenosis) is found rare in humans. The concentration and chemical form of it determines its toxicity. Among the most toxic compounds of selenium, selenate and selenomethionine are the important ones. At the same time due to its insolubility selenium sulphide is much less toxic [6]. Inorganic and organic Se are more toxic and lower biocompatibility than Se(NPs) [4].

Selenium nanoparticle has been used as a therapeutic agent as it is effective in growth inhibition of pathogenic microbes [7]. It has proven its antimicrobial properties against bacteria, fungi and virus. Its effect on bacterial infection is more important because the antibiotic

resistance that they have developed forced the people to overuse high concentration of antibiotics. In the market there are several NPs which are being currently used for its antibacterial properties. They include several metalloids and metal-based NPs (e.g., Silver NPs). But their high dosage usage or prolonged usage has brought many adverse effects on the health of the patients [4].

1. Selenium compounds

Selenium compounds are essential for the human health since they influence in the physiological functions of the body. This metalloid modulates the functions of many regulatory proteins that are present in the signal transduction [8]. This is helps in the inflammatory activities. Thus it holds critical effect on immune function, controlling inflammation, improving mammary gland health [9]. That includes adjustment of immune system activity and ROS control. A variety of selenoproteins and enzymes for example glutathione peroxidases and thioredoxin reductases has selenium as an important structural component. These selenoproteins influence the antioxidation, immune-modulation, metabolic cycling, detoxification, cellular homeostasis of the body [9]. So, the daily intake of Se into the body has to be controlled. The quantity that has to be taken depends on many things and that include sex, physical conditions etc. Some examples of recommended daily allowance according to European Food Safety Authority are listed below [4]:

60 µg/day – normal women
70 µg/day – men
75 µg/day – lactating women
65 µg/day – pregnant women

Approximately 20 µg/day – least quantity to prevent dilated cardiomyopathy (Keshan disease in adults)

The Selenium bioavailability is higher in animal products than in vegetables. SeMet (selenomethionine) is present in both animals and plants and selenocysteine is generally found in animal products. Its supplementation is found to be effective against the diseases like chronic metabolic disorders (diabetes, hyperlipidemia, and hyperglycemia), male reproduction and tumours [9]. In reproductive system, supplementation of Se can decrease the quantity of abnormal sperm in mice and could enhance the viability of Sertoli cells [4].

It has an important role in male fertility, reproduction and pregnancy. Miscarriage episodes and other pregnancy related complications (e.g., gestation diabetes, preterm labor, and preeclampsia) can be linked to the low levels of plasmatic Se [4]. At the same time Se proved itself to be an intracellular antioxidant in Leydig cells and neutralizes the H_2O_2 when the testosterone biosynthesis occurs [4]. The supplementation of Se can decrease the quantity of abnormal sperm in mice and could enhance the viability of Sertoli cells. Due to its antioxidant properties the expression of essential protein components is also affected [4]. Juvenile cardiomyopathy and myopathy is due to the deficiency of selenium [9].

2. Selenium Nanoparticles

2.1.Synthesis

As mentioned above SeNPs can be synthesized by 3 methods and they are physical, chemical, biological methods. The chemical method is considered as unsafe in many situations because it involves the use of agents to induce the catalytic reduction of ionic Se. So, it makes use of high temperature, acidic pH and other harmful chemicals [4].

The physical method uses different approaches. Some of them are photo-thermal-assisted synthesis approach, electrodeposition technique, PLA, microwave synthesis etc. But their usage is less than chemical method [4]. Gamma radiations are the easiest and most effective method used for the synthesis of NPs since it can be done in room temperature without any pressure [10].

The biological method or biosynthesis method is also called as green chemistry. This method reduces the selenate or selenite to elemental Se using biological method. It makes use of bacteria, fungi, plants, algae and yeast as the catalyst for the synthesis. The reduction of it is caused by the compounds that are present in these bio-organisms. They are flavonoids, amines, alcohols, phenols, proteins, aldehydes. This can lead to an eco-friendly, nontoxic and inexpensive production. It can even provide several advantages over chemical and physical methods [4]. They include inexistence of extreme conditions, the rapid growth rate of the microorganisms used, low toxicity, eco-friendly, economic, common culture procedures. They even have unique spectroscopic characteristics which can help in characterization process. The SeNPs which are synthesized may get surrounded by the macromolecules like enzymes, cellular residues, membrane phospholipids and proteins. It can be seen in elemental analysis assays by the presence of C, P, O and S [4].

2.2.Physical Properties

The method used for the synthesis and used and the compounds used for its stabilization or functionalization determine the properties of the SeNPs. The characteristics of a nanoparticle include its shape, structure and size. These characteristics are influenced by the parameters during their synthesis and storage. They include temperature, pH of the reaction mixture, concentration, nature of biomolecules [4].

The colour of SeNPs is ranging from pink, orange and red. So, during the synthesis the Se oxyanions get reduced to elemental Se which causes the colour change. This is due to the Surface Plasmon Resonance (SPR) affect [11]. The X-ray analysis identified hexagonal ring lattice in SeNPs. The formation of these structures seems not to be related to the shape of SeNPs or its production method. Because this type of crystal arrangement is found in both chemical and biological method [4]. The trigonal SeNPs formation is more related to its physical synthesis method. And its charge is found to be negative but that can also be modified by some compounds like chitosan which can change it into positive. The shape of these nanoparticles is influenced by

production method, reaction temperature, solvents used, storage conditions, Se reducing agent, interactions among them and the coating agent used [4].

3. Antimicrobial activity against FEMALE RELATED disorders

3.1.Disorders

3.2.Urinary Tract infection (UTI)

The intestinal area of humans and many animals are observed to have the presence of *Staphylococcus aureus* and *Escherichia coli*. E. coli is known to cause intestinal diseases and many additional infections which includes intestinal dysfunctions and UTI. Bacterial biofilms play an important role in UTI. The pathogenic microorganisms tend to forms biofilm in areas with moisture because of better nutrition and surface connections. This also helps in protecting the population from the environmental pressure [4]. The matured bacterial film has resistance to the host protection responses, bacteriophages and varieties of bactericides. This property is due to the extracellular polysaccharides that are produced by these cells [10]. The UTI is a common infection found in women. But by the usage of different drugs, MRD (multidrug resistant) microbes generation happened in those areas which made it difficult to treat. It was proved by [10] that SeNPs have the antibacterial property against the bacteria like *Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa, Escherichia coli* and pathogenic yeast *Candida albicans*) that tends to cause UTI. The incorporation of antimicrobials into these NPs showed a better result.

3.3.Mastitis

Mastitis is a condition where there is an inflammation in the mammary gland due to infection. The main factors that are found to be responsible for this condition are categorized into 3. They are environmental conditions, host resistance and the causative agents [12]. It causes a feeding problem to most of the mammalian species [13]. It affects cows' udder in a great extent which indirectly affects the dairy industry especially in the areas where the milk and milk products are rare like Ethiopia [14]. In humans, mastitis is found in both lactating and nonlactating women causing breast abscess and septic fever [15].

Bovine mastitis

Among the different factors which leads to this disease, deficiency of minerals is an important one [9][16]. Because they can actively influence the immune system. The infection is caused by the infection of bacteria (*Streptococcus agalactiae* and *Staphylococcus aureus* are the primarily known cause), fungi, algae, yeast in bovine [9]. These pathogens attack the udder and releases the substances which will cause the inflammation, milk production reduction and milk quality alteration [17]. The selenium affects the immune and inflammatory systems by influencing the differential expression of exosomal mRNAs of the significant genes in bovine mastitis [9]. The usage of antibiotics have the side effect which includes the presence of the trace

of antibiotics in the produced milk and also generates the antibiotic resistant strains [9]. It was found in bovine, that by the supplementation of Se, the lymphocyte function is affected by the alteration of the expression of high-affinity IL-3 receptors in the body [9]. An increase in the concentration of IgM and IgG was also found in the colostrum from cows which were fed with a high dose of selenium [9].

In a study, it was proved that by the administration of organic selenium, the mastitis in rats which was induced by S. aureus could be reduced. It was done by inhibiting the activation of NF- κB, expression of many inflammatory cytokines and MAPK signalling pathways [9]. In a research, the differences between mRNA transcriptome of exosomes extracted from MAC-T bovine mammary epithelial cells which are having selenium deficiency and the ones with supplementation of selenium were analysed by RNA-Seq [9]. The exosomes have many biological functions which include the immunoregulation and anti- inflammatory activities and transporting genetic materials by transferring several genetic materials to target cells and then influencing their metabolism [9]. It was found that the novel communication of exosomes of the MAC-T cells which were supplemented with selenium modulate cell functions through differential expression of the mRNAs of the genes which are important for bovine mastitis. From the microarray studies, it was proved that many selenoproteins mRNAs are suppressed in immune cells when there is a deficiency of selenium [9]. The mRNA's involvement in inflammatory signalling pathways is decreased by the low-level concentration of selenium [9].

The microorganisms which lead to mastitis is broadly classified into 2 categories and they are contagious pathogens (generally during the milking process, they spread from cow to cow) and environmental pathogens (found in the habitat of cows). Some of the examples for contagious pathogens are *Streptococcus agalactiae, Staphylococcus aureus, Corynebacterium bovis, Mycoplasma* species [14]. And the examples for environmental pathogens are *Streptococcus uberis, E.coli, Streptococcus dysgalactiae, Klebsiella* species then some other catalase negative cocci and Gram positive bacteria [17] [14].

In a study done by Hassan *et al.*, the *Staphylococcus aureus* and *Escherichia coli* were obtained as the major bacteria while *Candida albicans* and *Aspergillus flavus* were the prominent fungus from the mastitis affected buffalo's milk [18]. By the application of Selenium nanoparticles towards these microbes, antibacterial property was observed. They concluded that the death of the cells is due to the leakage in the inter cellular components. That happened because these NPs damaged and ruptured the cell wall. Membrane damage and some pits were observed when they were subjected to SEM (Scanning Electron Microscope). These NPs were also observed to be adhered to the respiratory sequence of cytoplasm.

HUMAN

About 33% of lactating women are suffering from mastitis and this condition is usually found during the first six months of postpartum. The main reason for this found in them is milk stasis and infection [15]. It was proved by many scientists that most of the mastitis are caused by the change in microbiome in the mammary gland. The microbial dysbiosis in the human milk was observed [19]. Most of the bacteria which leads to mastitis is capable of producing biofilm.

In a study the class belonging to *Bacilli* was found to be present at 69.08% to 74.07% and the genus *Staphylococcus* was found to be at 62.53%- 70.97% in acute mastitis samples [20]. *S. aureus* were found at a lower diversity, i.e., 60.9%-67.2%. 3 classes were seen as dominant in sub-acute mastitis by [20]. They were *Gammaproteobacteria* (17.15%-32.39%), *Bacilli* (10.00%- 35.07%) and *Alphaproteobacteria* (12.03%- 25.43%). In another experiment, S. aureus appeared to be one of the causes of abscess in breast [21].

Staphylococcus aureus is found to be the major etiological agent responsible for acute mastitis while *Staphylococcus epidermis* is responsible for subacute mastitis. The causative agent for human granulomatous mastitis is recognized as *Corynebacterium* species [15].

4.1.3 Endometritis

Endometritis is the condition when the inner lining of the uterus (endometrium) is inflamed due to infection. It is a reproductive obstacle disease. The mucous or purulent inflammation in the uterine tissues happens [22]. This infection affects animals and also humans leading to decrease in their productivity and fertility [8]. The main source through which this infection occurs is from the environment. They get access through the genital tract during parturition and also through the relaxed perineum, vulva and dilated cervix during the puerperium [22]. *Staphylococcus aureus* is the predominant pathogen affecting endometritis [8][23]. Some studies proved that Selenium showed anti-inflammatory effect on this uterine inflammatory damage by decreasing the expression of tumor necrosis factor alpha tumor (TNF-α) and interleukin-6 (IL-6) [8].

Taylorella equigenitalis, Pseudomonas aeruginosa and *Klebsiella pneumoniae* were found to be the major venereal pathogens that cause acute endometritis and low fertility in mares. The bacteria like β-haemolytic *Streptococci, Escherichia coli* and *Staphylococcus aureus* were found from the genital tracts of stallion. In another study the predominant fungi that lead to endometritis in cattle and buffalo were *Penicillium* species and *Aspergillus fumigatus* [24]. *Candida albicans* was found to be the cause of endometritis in water buffalo in the study conducted by M Pal [25].

4.1.4 Vaginitis

Vaginitis is a condition where the inflammation of vagina occurs with some discharge, itching and pain. The reason for this is usually the alteration in the normal balance in the vaginal bacteria. The predominant microorganism that was obtained from the bacterial vaginosis (BV)

was *Gardnerella*. Many studies have proved the contribution of *G. vaginalis* in BV[26]. In another study, the major bacteria identified from the culture from women who had BV were *G. vaginalis* (pathogenic aerobic), and some anaerobic bacteria like *Prevotella, Bacteroides, and Peptostreptococcus* species [27]. The vaginitis that is caused by fugus is found to affect 75% of the women in any time if their lives. In many studies 85% -90% of the vaginal samples had *Candida albicans* [28].

Antimicrobial activity

The parameters that influence the antimicrobial properties include its size, elemental composition, purity, actual shape and surface area. It also depends on the concentration of SeNPs used [11]. The elemental SeNPs has larger surface to volume ratio. Being in the nanoscale they can effortlessly join the biological organisms like bacteria and yeast. Thus, by the usage of synthesized Se NPs an antimicrobial potential can be generated without developing antimicrobial resistance unlike general synthetic antimicrobial agents [10]. In the above mentioned female related disorders, the microorganisms like Staphylococcus aureus, *Klebsiella pneumoniae, Escherichia coli, Staphylococcus epidermis* were found to be the common cause for the disorders. So, the effect of SeNPs on these microorganisms has to be studied.

SeNPs are found to have antimicrobial activity against the microbes like bacteria, algae, fungi, virus. It is shown bactericidal activity against Methicillin- resistant *Staphylococcus aureus* (MRSA) at 1ppm [4]. Through functionalization, the targeting of SeNPs towards bacterial cells can be improved. Se-MSNPs proved to have better antibacterial activity for MRSA than bare SeNPs. But this is no effective against E. coli. Its antibacterial effect was also seen in *Staphylococcus epidermidis, Pseudomonas aeruginosa,* [4].

In general, the antibacterial potential of SeNPs is due to: the metabolic disfunction due to decreasing of ATP concentrations, increase in concentration of ROS in the intracellular area which causes oxidation stress [4]. This leads to the loss of bacterial resistance to SeNPs. Then the inhibition of protein synthesis and the DNA mutation and damage, depolarization and destruction of the bacterial membrane results in its antibacterial activity. A biomolecule that contains SeNPs and lysozyme (nanohybrid) can act against gram-positive bacteria. This has shown a synergic effect on antibacterial activity [4]. The lysozyme present in it can act against the gram-positive bacteria by hydrolysing 1,4- β-linkages of its cell wall. Because it acts as β-glucosidase. But because of the presence of lipopolysaccharide, it will not be effective. Since the nanoparticles have negative charge, there will be a repulsion effect by the lipopolysaccharide gram-negative bacteria (e.g., *E. coli*). That is the reason why its action against E. coli is effective [4].

In a study done by Soumya Menon and team, it was found that the Selenium NPs extracted from ginger had suppressing effect on bacterial growth. The bacteria those were tested

were Gram positive (*B. subtilis* and *S. aureus*) and Gram negative (*Serratia* sp., *Klebsiella* sp., *Proteus sp*., and *E. coli*). Its inhibition zones were found to be in the order *Proteus sp*., (20 ± 0.5mm), *Serratia* sp., (17 ± 0.7mm), *Escherichia coli* (12± 0.5mm), *Klebsiella* sp., (9± 0.8mm), *S. aureus* (7 ± 0.6mm) and *B. subtilis* (5 ± 0.2mm)[11].

In another study done by Mojtaba Shakibaie and team, the antibacterial property of SeNPs on biofilms of bacteria were analyzed. The biofilms of *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Proteus mirabilis*. The SeNPs inhibited the biofilm of *Staphylococcus aureus* by 59.3 ± 2.1%. The *P. mirabilis* biofilm was found to get decreased to 53.4 ± 2.3% and *P. aeruginosa* was decreased to 34.3 ± 1.4% [29]. The study done by Kristyna Cihalova showed that the biofilm of *S. aureus* was inhibited up to 99% ± 7% and up to 94% ± 4% for MRSA [30]. On treating Candida sp., with SeNPs the biofilm formation was inhibited and also to disaggregated the mature glycocalyx[31].

Conclusion:

This study was towards the effect of SeNPs on microbes resulting in female disorders. Its effect on bacteria as well as fungi were studied and was found to be effective against them. By the application of antibiotics, the antibiotic resistant strains were generated which is more difficult to cure. The advantage of using SeNPs is that, it is mineral which is essential for the body and at the same time it will not lead to the generation of antibiotic resistant strains. Since the nanoparticles are having more surface area to volume ratio, they are effective on the biofilms also. Immense possibilities are there in handing female disorders caused by microbes with SeNPs which are yet to be studied.

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APPLICATION OF AI-BASED TECHNOLOGIES IN THE HEALTHCARE SECTOR: OPPORTUNITIES, CHALLENGES AND ITS IMPACT - REVIEW

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Abstract:

Nowadays, Artificial Intelligence offers a great number of benefits over traditional methods of analytics and clinical decision making practices. Not only that, learning algorithms has become more and more accurate and perfect as they Learning algorithms can become more precise and accurate as they interrelate with care processes, training data, patient outcomes, treatment variability allowing humans to secure unusual insights into diagnostics. This survey investigates the present situation of artificial intelligence-based technologies in the healthcare sector applications and their impact. The outcomes state that major hospitals are now using AI-enabled systems to enhance medical employees in treatment activities and patient diagnosis for a broad choice of diseases. In addition to that, artificial intelligence systems are building an impact on improving the managerial activities of hospitals and effectiveness of nursing. AI applications provide both the challenges and new opportunities to overcome while it's being embraced while AI is being embraced optimistically by healthcare providers. The aim of this chapter is to investigates the recent challenges and provide an outlook on the benefits, impact and the future opportunities of artificial intelligence applications in healthcare sectors. It is well clear that fast advances of AI and related technologies will assist healthcare providers to create a new significance for their patients and improve the competence of their equipped processes. However, effectual applications of AI will involve efficient strategies and planning to renovate the entire healthcare service and operations to obtain the advantages of what technologies provides.

Keywords: AI-based technology; opportunities, challenges; impact; healthcare industry

Introduction:

Alan Turing (1950) was one of the first computer and AI pioneers. The "Turing test" has been founded on the idea that a computer's intelligent behavior is a capability in cognitive tasks for achieving human level performance. [1] The AI interest increased in the 1980s and 1990s. In many clinical situations in the healthcare system artificial smart approaches were employed such as fumigation expert systems, the Bayesian networks, artificial neural networks and hybrid smart

systems. In 2016, in comparison to other industries, the largest part of AI research expenditure was in healthcare applications. [2]

AI may be duplicated into two kinds in medicine: virtual and physical. [3] The virtual section extends from electronic health record systems applications to neural network orientation in treatment decisions. The physical portion covers robot operations, intelligent prostheses for the disabled and aged.

The evidence-based medicine is centred on establishing relationships and patterns from the current database of information to generate clinical correlations and insights. We utilized statistical approaches traditionally to identify these patterns and correlations. Diagnosing a patient using two major approaches - flowcharts and the database approach is learned by computers. The flow diagram technique consists on translating the history procedure, that is, a physician who asks a number of questions and then makes a likely diagnosis by integrating the provided system of symptoms. This calls for data to be fed into machine-based cloud networks that take into account the vast variety of symptoms and disease processes in normal medical practise. The results of this technique are restricted since the machines cannot see and collect information that a doctor can only notice during a patient's meeting.

In contrast the database technique uses the deep study or pattern recognition concept that teaches a computer to identify whether symptoms or clinically/radiologically specific photos are similar via repeating algorithms. The artificial brain project announced by Google in 2012 is one example of this technique. With 10 million YouTube videos this system has educated users to detect cats with efficiency by examining more and more pictures. It could anticipate a cat picture with 75 percent precision after 3 days of learning. [4, 5].

Literature review, methodology and analysis:

Literature review

Various studies in different regions of the globe have been done to measure AI perception. Various types of specializations and medical experts were polled and interviewed for their views on AI and the best path ahead in its deployment, use and relevance. According to a study by Lai et al (2020) France, 40 persons, including physicians, industry stakeholders, health IA researchers, members of regulators, and a few not directly engaged, were interviewees. In general, the doctors surveyed had a positive view of AI and its instruments and the potential benefits for patients in reducing time and providing timely warnings. AI could help to improve care, increase patient safety and make it more cost-effective. Some doctors believed AI might change their practices and patient care, while others stated that the continued advancements in medical practise will simply be continued.

In terms of application and execution of AI technologies, radiology and radiation therapy are arguably the most advanced expertise. In a research done by Giansanti et al, (2020), the contact with the radiology infrastructure was investigated by 182 health professionals and

medical radiology technicians directly. Three key themes have been investigated: 1. AI development grade for COVID-19 pandemic, 2. radiologically diagnostic application of AI areas to participants would invest in the pandemic of COVID-19 and 3. The views of participants on the future of the CO VID-19 pandemic in digital radiography. The overwhelming answer was to consider chest CT and radiography diagnostic areas of major research and training as well as the investment in artificial intelligence domains. Finally, 87% said AI's further contribution would be provided, 10% believed it would replace human choice and 3% felt it had no future. Some participants were also concerned about a reduction in the professions owing to probable automation among others, as well as open-ended remarks. Privacy and confidentiality concerns have also been raised.

Gillan et al (2018) have again carried out a study, which included interviews with four distinct sorts of specialists in radiology. The study concluded that patient care was perceived to be utilizing AI. The overwhelming consensus was that AI would increase quality of treatment. Participants discussed efficiency, availability of fresh and accessible data, clinical decision-making value and possible progress towards increased accuracy and care complexity. Only the disadvantages of AI quality, such as the AI-concept as an unproven, invaluable black box have disturbed some of the responders. The quality of AI output is thus only as high as the inputs of data.

One group of radiation therapists claimed that there was a need for lower levels of treatment planning and noted an overall fear of job loss. However, some thought that some of the improvements introduced by AI would better modify their responsibilities and could completely use the breadth of their profession. There was also discussion on the need for new skills and training. Finally, in order to operate responsibly with AI in the therapeutic setting all groups referred to as require for awareness of the principles, functions and limits of AI.

Castagno and Khalifa (2020) studied health workers' views towards AI and carried out a survey of health workers, doctors, therapeutic managers and others on the subject of job replacements and worries about doctors losing employment for AI. The survey was answered by 98 UK experts. They found that 80% believed that AI may offer major privacy problems and 40% considered that AI could be even more deadly than nuclear weapons. Nearly 78% of participants believed that AI might be useful for their respective sectors or highly helpful and 10% were worried that AI will replace them at the cost of their work. Interestingly enough, 72 percent indicated they were not concerned that AI would make them lose their jobs, which varies from the results of other study projects on AI.

For example, Surveys conducted by Smith and Anderson (2017) determined that almost 70% of Americans anticipate that in the next 50 years, robots and computers will carry out most of the work that humans do now and that 72% are worried about such a future. The reason could be the belief that AI is devoid of human emotions or empathy expressions and therefore cannot

engage in the multi-layered interaction necessary to reassure patients and gain their trust (Krittanawong, 2018). The results of Castagno and Khalifa's (2020) survey also demonstrated a general lack of knowledge on the subject of AI and of awareness of its applications.

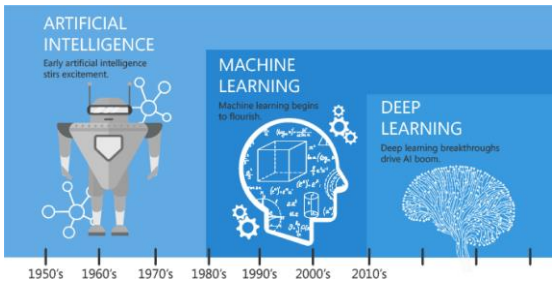


Figure 1. Evolution of Artificial Intelligence

Methodology

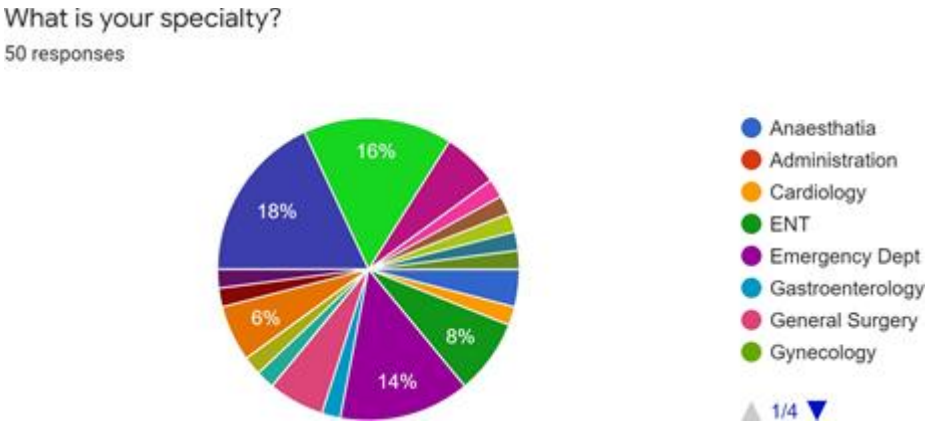
This section of the research paper discusses and explains the various research methodologies employed and how they were used and utilized so that we could answer our topic of inquiry. The research technique utilized in this study was existent where university research in the field of AI substituting doctors in the healthcare sector was done. Qualitative and quantitative research was carried out, as our conclusions were supported by both data and words. We have searched academic sources for websites such Google Scholar and Worldcat to gain and uncover data that supports our results. After that, the resources collected were analyzed so they could be used to support our findings and add value to our research work. In this article both primary and secondary sources have been utilized, the secondary sources have been scholarly research on the theme, and 8 main sources have surveyed 50 physicians in the UAE asking them questions on AI in their area, as previously described.

In the analysis section, the questions posed in the survey and their answers will be provided in depth. In order to obtain both qualitative and quantitative research data, we have incorporated short response questions and evaluation questions in our survey. To fit the hectic schedule of physicians at the India, more questions are not included in the survey and the fewer authentic replies are possible. The findings of the survey are used to illustrate how much and to what degree AI has been used to aid physicians at work and if AI is effective in supporting physicians or making their lives difficult.

Analysis

As you already know, we performed a survey with a set of 8 questions emailed to doctors to find out the healthcare industry's influence on artificial intelligence. First, we asked the physicians about their department. This was significant as it would help us understand whether there was a certain health department ahead when the Artificial Intelligence was adopted. For example, out the 9 doctors with a specialty in radiology, 8 persons are now working at their workplace with Artificial Intelligence. While just one doctor had Artificial Intelligence in his job, dentistry, which had the second largest number of responders with 8. This could be largely

attributable to the use of electronics and computers by a majority of a radiologist. And therefore integration with Artificial Intelligence would be straightforward. On the other hand, dentists have a "hand" approach to their work, and when compared to radiologists, their physical interaction between the doctor and a patient is higher.



For the second question, the majority of physicians currently have little experience to artificial intelligence. To be precise, 32 people replied negatively, while just 18 responded positively. This can partially be explained by patients' unwillingness to be treated or diagnosed with AI since they feel that their medical requirements are unique (Longoni & Morewedge, 2019). The study supports this logic, as most of those who utilize AI have no direct interaction with patients and only surgeons and radiologist use them. However the poll also shows that there has been an increase in AI acceptability, as a few of gynecologists and practitioners have also employed AI in their workplaces, who deal extensively with patients.

On the third issue, most people think that AI can provide faster and more accurate diagnostic results and this is no surprise, since today's computer systems are quite advanced and have a lot faster processing capacity than they were 10 or even 5 years ago.

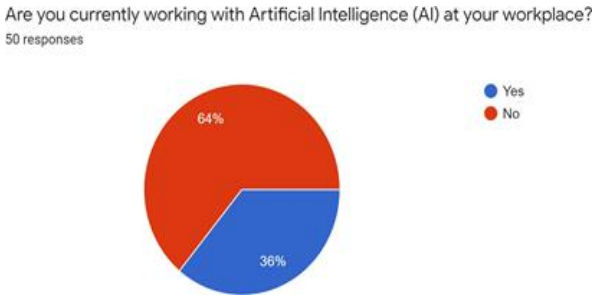
In relation to the fourth issue, 43 participants indicated in particular that AI will not replace physicians on the workplace. In assessing its reaction, 2 factors should be taken into account: timeframe and AI exposure. In the next ten years, may we see physicians fully replaced? I doubt it very much. From 20 to 30 years, the fact that AI will dominate this environment would be more feasible since rules would be eased, and a far broader range of individuals would be simpler to reach. Secondly, we need to remember that AIs employed in healthcare now carry out relatively simple tasks or are mostly not used from the second question.

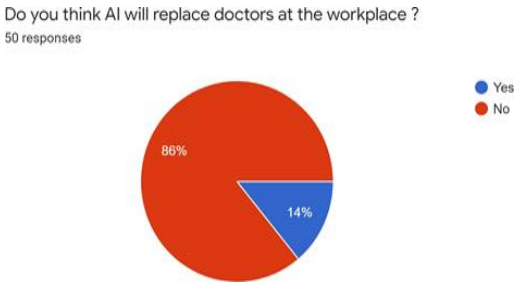
In the fifth question, most respondents, 41, agree that AI will contribute to reducing the number of physicians involved. That is because AI would help to look after the paperwork while moving from patient to patient rapidly.

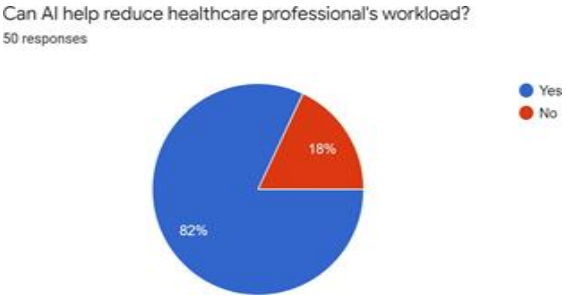
Question 6 is particular to the group that now uses AI; nonetheless, of the total of 50 correspondents, half report moderate workplace influence. Despite the fact that greater responders from radiologists are included in the overall number of physicians polled, only 36%

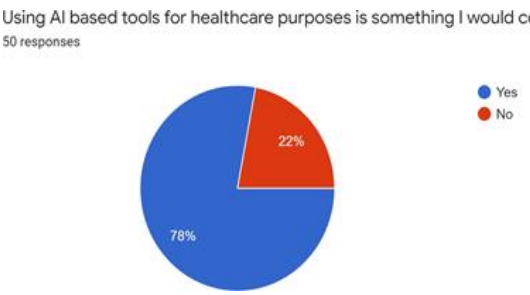
of the respondents in the study use AI. 78% of respondents would consider their place of work utilizing AI-based technologies. This would be a welcome idea to undertake more research and development in this sector for the AI-based healthcare firms. AI is not flexible to apply to every patient when the 1 to 5 options are offered on a Likert scale with a score of 3 or above, 84 percent of respondents consider. These are the interpretations which we get from the survey questions which are responded by different health professionals in the UAE.

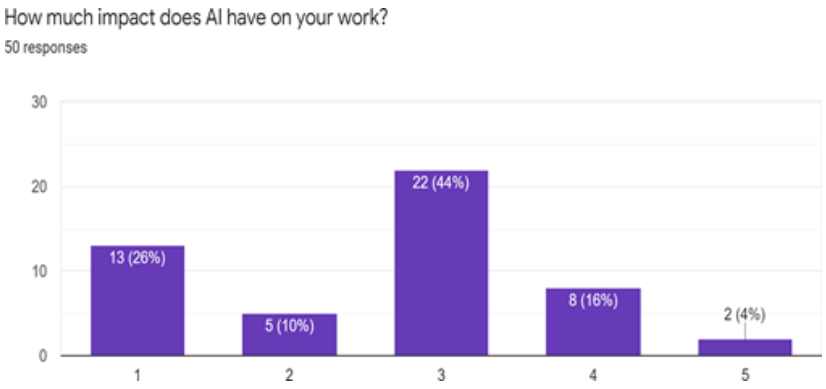
The findings of the survey and the questionnaires are given in the following images:

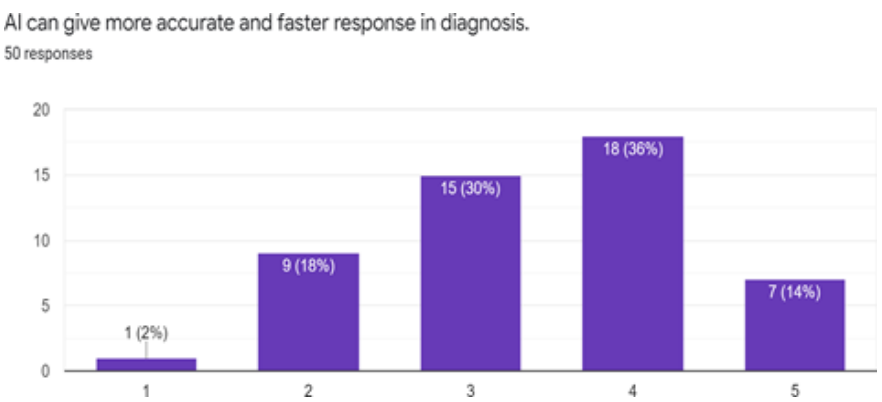


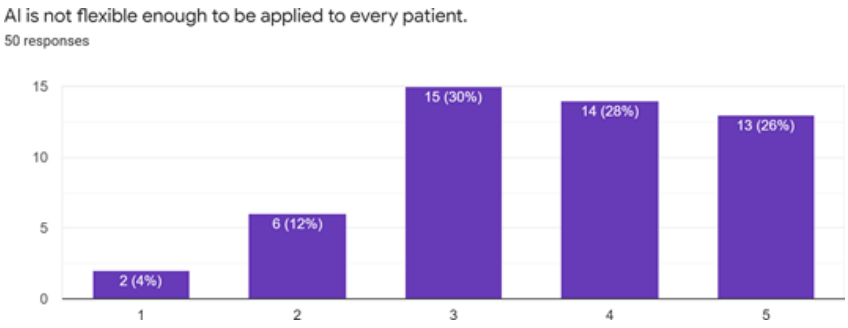












Discussion and Limitations

Discussion

AI is becoming a public health sector and will have a significant influence on all aspects of primary care. The computer programmes that are AI-enabled will assist primary care providers better identify patients that need more attention, providing unique customized regimens. Primary healthcare professionals may utilize AI to take notes, evaluate talks with patients and enter the information requested straight into EHR systems. These programmes are designed to gather and analyse patient information and give primary care clinicians' insight into the medical requirements of the patient.

A survey done in 2016[6] revealed that doctors spent 27% of their office days with their patients on a direct clinical face and spent 49.2% of their office day records and work at the hospitals. When doctors spend 52.9% of their time on EHR and other tasks in the examination room with patients. Finally, doctors who have utilized the help of documentation, such as dictatorial care and medical services, worked with patients more directly than those who did not use the services. In addition to reducing manual work and freeing up primary care physicians, growing use of AI in medicine also enhances productivity, precision and efficiency.

It takes years and millions of dollars to look for and develop pharmacological medicines against a certain illness through clinical trials. A recent example was that AI was utilized for screening current drugs that might be used to combat the Ebola virus threat that could take years for otherwise to be treated. We could adopt the new notion of "precise medicine" with the aid of AI.

Some researches have shown AI systems in which dermatologists have been able to supervise the proper classification of worrisome skin damage. [7] Because AI systems may learn more from subsequent instances and can expose themselves in minutes to numerous cases, which much outweigh those a doctor may assess in one death. In cases where specialists commonly differ, such as pulmonary TB identification in thoracic x-rays, AI based decision-making techniques will apply. [8]

This new age of AI-enhanced practise has as many critics as advocates [Figure 2]. The growing use of technology has lowered the amount of career prospects that concern many doctors and doctors.

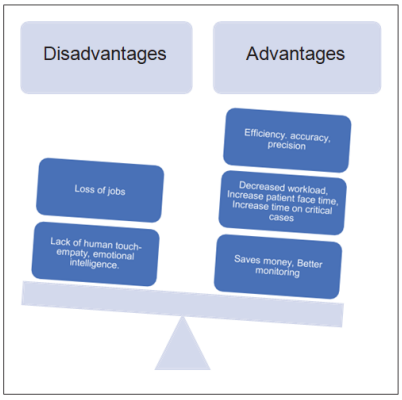


Figure 2: Advantages and disadvantages of artificial intelligence in medicine

A Digital Mammography DREAM Challenge in 2016 was conducted in which many computer networks were joined and a revision of 640,000 digital mammograins was intended to develop an AI-based system. The greatest thing that was obtained was a specificity of 0.81; the sensitivity was 0.80, the area below the curve of the recipient operator was 0.87; that is almost 10% lower. [9] In summary, AI has potential, but AI is unlikely to replace doctors correctly.

In the future, AI is an important component of medicine. Therefore, training the new generation of trainees in the field of AI's ideas and application and how to interact with machines effectively in a workplace for improved productivity, together with fostering soft skills such as empathy in these areas is vital.

Limitations

Some limitations of this study are crucial to mention. One restriction is that we have a very small sample size of 50 and thus statistical relevance in replies and the variations between responses, in particular between occupations, was difficult to identify. The rationale for the sample being limited is because people are encouraged to take the survey rather than cloud answers. Secondly, there is the problem of selection bias, as some respondents could have been interested in AI and have thus given their pre-conceived concepts of AI a favorable answer. Finally, our interviewees came from several specialties instead of one. Some research in the past have only focused on professional radiologist since the field in the use of AI is most progressed.

Conclusion:

The future AI breakthroughs and the new unidentified area in the medicine world is going into is crucial to primary care providers. The aim is to create a sensitive mutually advantageous balance between efficient use of automation, AI and the human strengths and the assessment of qualified primary care practitioners. This is important since a total replacement of AI people in the medical area might otherwise hinder the advantages.

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MOST COMMON DISEASES: DIABETES AND OBESITY, THEIR TYPES, SYMPTOMS AND CAUSES

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Diabetes and obesity resistance is tied to a powerful relationship. In diabetes, the β-islet cells of the pancreas get weakened, due to which the body is not able to control the blood glucose. If the β-islet cells present in the pancreas not working properly, Diabetes becomes more prevalent which leads to insulin resistance. Acquiring weight and BMI are interrelated and thus cause diabetes. Diabetes and obesity have a strong relationship. One led to the causing of the other. However, the choices of drugs for the combined treatment of diabetes and obesity are few and also limited.

Introduction:

Diabetes Mellitus is a group of chronic disorders when a diseased person's blood glucose level increases. The increase in blood glucose is mainly due to two reasons i.e. if the body does not produce an appropriate amount of insulin or the body is not able to give respond to the insulin produced by the pancreas. The prior symptoms of the diabetic patient are i.) polyuria, ii.) polydipsia and iii.) polyphagia.

All over the world diabetes patients number expected to rise from 171million in 2000 to 366 million in 2030 (Wild *et al*., 2004). According to WHO, 220 million patients with diabetes are recorded all over the world. These studies came to the conclusion that due changes in way of living, eating habits and environmental factors led to an unexpected increase in diabetes. (De Meytsand Whittaker, 2002). The word 'Diabetes' is derived from the Greek word for 'pipe-like' because essential nutrients of the body start to pass through the system instead of being utilized, while 'Mellitus' is the Latin word for 'honey' or 'sweet'.

How does diabetes affect the body?

Proper Blood glucose level what the healthy person has is not maintained by the body of diabetic patients. One of the main sources of energy in our body is Glucose. Ups and downs in blood glucose levels in the body give birth to short-duration and long-duration health-related problems.

To get the energy to do work body requires food and that can be met when our body converts glucose (sugar) from food into energy. For the conversion of glucose into food or we can say energy a hormone secreted by the pancreas called Insulin is required. In diabetic patients, either insulin is no longer produced or not produced in the required amounts by the body. When a diabetic person eats glucose-rich food then their body is not able to convert it into energy. As a result, the glucose remains as it is in the blood resulting in high blood glucose levels. After eating, the glucose is moving in your blood in your body. Blood glucose level is commonly called glycemia. The only remedy to keep a check on Blood glucose levels and further diabetes is self-care and treatment.

Types of Diabetes:

1. **Type 1 Diabetes**

   In type I Diabetes body is not able to produce an equal amount of insulin. This type of diabetes is also called early-stage diabetes and insulin-dependent diabetes. Type 1 diabetes is called as early onset diabetes as it occurs in a person at 40-years-old age i.e., in early adulthood or teenager. Due to its early onset, Patients will need to take insulin injections for the rest of their life. These patients also have to keep a check on proper blood-glucose levels through blood tests and following a prescribed diet.

2. **Type 2 Diabetes**

   In Type 2 Diabetes, the body is not able to produce enough insulin or the body cells become resistant to insulin. Doing a lot of exercise, healthy diet, maintaining blood glucose level, losing excess fat or losing weight is the healthy habits by which one can control type 2 diabetes. In spite of this type 2 diabetes is a gradually progressive disease in which a patient's condition became worse by which a patient leads to take insulin in a tablet form for the rest of their whole life.

   Acquiring excess weight more than a person's BMI, Physical inactivity, and irregular or bad feeding habits are the symptoms to welcome type 2 diabetes and the chances of acquiring type 2 diabetes increase with the increase in age.

3. **GestationalDiabetes**

   Gestational diabetes as the word indicates that this type of diabetes is related to females in their gestation period i.e. pregnancy period. Females during pregnancy suffer from this type of diabetes.

   Females are mainly affected during the gestation period. Some of the ladies have very high levels of glucose output in the blood and its decomposition in the various cell does not take place due to less production of insulin resulting in the rising of glucose levels.

This type of diabetic patient can get control this by doing easy and safe exercise and a balanced diet. Some ayurvedic or light allopathic medication can also be taken by consulting a ladies' doctor.

Gestational diabetes can be controlled and diagnosed soon in the pregnancy period otherwise it can raise complications and risks during delivery.

Persons suffering from any type of diabetes require to treat with insulin at their disease stage.

Causes of Diabetes

Less/inappropriate production of insulin required by the body, body cells' inability to use insulin accordingly which leads to hyperglycemia which in turn leads to diabetes.

- Diabetes affects the cells of muscle and fat tissue due to which there is insulin resistance. This is the initiatory problem in type 2 diabetes.
- Inappropriate insulin, producing less insulin by beta cells of the pancreas is the initiatory point of type 1 diabetes.

When the beta cell present in the pancreas decreases the blood sugar of the patient increases in case of type 2 diabetes.

In type 2 diabetes, there also is a steady decline of beta cells that adds to the process of elevated blood sugars. Essentially, if someone is resistant to insulin, the body can increase the production of insulin and the level of resistance is met. If the production of insulin decreases or the insulin cannot be released dynamically it leads to hyperglycemia i.e. increased blood glucose level.

Symptoms

- Being excessively thirsty
- Passing more urine
- Feeling tired and lethargic
- Always feeling hungry
- Having cuts that heal slowly
- Itching, skin infections
- Blurred vision
- Unexplained weight loss
- Mood swings
- Headaches
- Feeling dizzy
- Leg cramps

These symptoms may occur suddenly. If they occur, see a doctor. Through a simple test, a doctor can find out if they're the result of type 1 diabetes.

Symptoms of Type 2 Diabetes include:

- Being excessively thirsty
- Passing more urine
- Feeling tired and lethargic
- Always feeling hungry
- Having cuts that heal slowly
- Itching, skin infections
- Blurred vision
- Gradually putting on weight
- Mood swings
- Headaches
- Feeling dizzy
- Leg cramps

Obesity

When the fat cells present in the body increase or they can make their size large then normal growth of adipose tissue is hindered and abnormal growth is recorded which causes obesity. Obesity is shown by body mass index (BMI). If a person has a BMI of more than 30 then the person stands on the list of obese.

Obesity is considered a worldwide emerged and also emerging so vastly from children to every stage of life. It is common problem which gives rise o many other fatal problems. The main characteristic of obesity is the abnormal growth of adipose tissue due to an increase in fat accumulation in the body. Fatty mass accumulation directly refers to weight gain than normal by the affected person. Taking excess food than normal appetite or body needs, Intake of fast foods, lack of exercise and physical activity, genetic factors etc., are the root cause of obesity.

Obesity can be controlled by changes in food habits and regular exercise. Otherwise if the problem of obesity increases then it gives invitation to hypertension, diabetes mellitus, atherosclerosis, coronary artery diseases and many other diseases.

Causes of obesity

Dietary factors: Increased intake of energy, more than the body's requirement like:

• Taking snacks or eatables in between meals.
• Taking excess sweets, ice creams, and oily foods.
• Often eating fast foods.
• Increased numbers of feedings in infants.

Decreased physical activity: Due to a Lack of physical activity, the body of a person uses less energy and in turn increases the storage of the body.

Age: Obesity can occur at any age, increasing the occurrence of the increase in age. This is due to decreased physical activity with the increase in age.

Sex: Usually men gain weight between the age of 30 – 35 years whereas females are between the age of 45 – 50 years.

Genetic factors: 12 chromosomes and 20 genes are responsible for the onset of obesity.

Psychosocial factors:

• Depression
• Sedentary lifestyle
• Anxiety
• Frustration

Personal factors

Personal habits like

• Alcohol intake: increases appetite and decreases energy expenditure.

Secondary factors

It includes endocrine disorders like

• Hypothyroidism

• Cushing's syndrome

• Insulinoma

• Hypothalamic disorders

Types of obesity

Based on causes it is classified into the following types

1. Juvenile onset obesity – starts in childhood
2. Adult-onset obesity – starts in adulthood
3. Genetic Obesity
4. Drug-induced obesity
5. Endocrinal obesity
6. Psychosocial obesity

Based on the site of deposition of fat tissue it is classified into the following types

1. Generalized obesity: excess fat deposition will be uniform all over the body.
2. Android obesity: excess fat deposition takes place over the waist.
3. Gynoid obesity: excess fat deposition takes place over the hip and thighs.
4. Superior or central obesity: excess fat deposition over the face, neck and upper part of the trunk.

Complications

The complications of obesity are:

1. Hypertension
2. Hyperlipidemias
3. Diabetes mellitus
4. Atherosclerosis
5. Coronary artery diseases
6. Cerebrovascular accidents
7. Osteoarthritis
8. Cholelithiasis (gallbladder stones)
9. Depression
10. Gallbladder and colonic cancer

The pervasiveness of diabetes for all ages of persons all over the world was approx. 2.8% and 4.4% in 2000 and 2030 respectively. According to the anticipation India, China and the United States will comprise a large number of people suffering from diabetes by the year 2030. (Wild *et al*., 2004). Diabetes mellitus is defined as a more diabolic disease with increased blood glucose levels (hyperglycemia) resulting in problems occurring in insulin secretion and its action. (Alberti and Zimmet, 1998).

Diabetes mellitus can be detected in less apparent stages and before fasting, hyperglycemia appears, by the onset of glucose intolerance. According to WHO classification which is based on treatment variations, there are two major types of diabetes i) IDDM or type 1

(insulin-dependent diabetes mellitus), ii) NIDDM or type 2 (non-insulin-dependent diabetes mellitus) (Dash, 1999; Dunne *et al*., 2004). In both types of diabetes Type I diabetes can be diagnosed in the early stages i.e. childhood stages which is mainly represented by a loss of cells by an autoimmune process which leads to insulin deficiency. Resistance to insulin is common in Type 2 diabetes and it can be boosted by obesity which leads to insulin resistance. (Yanjnik *et al*., 2001).

From an estimate, it is recorded that only 5% of diabetic patients are suffering from Type 1 type of diabetes and the rest of the 95% of diabetic patients are suffering from Type 2 diabetes. Type 2 diabetes is always due to hereditary factors,

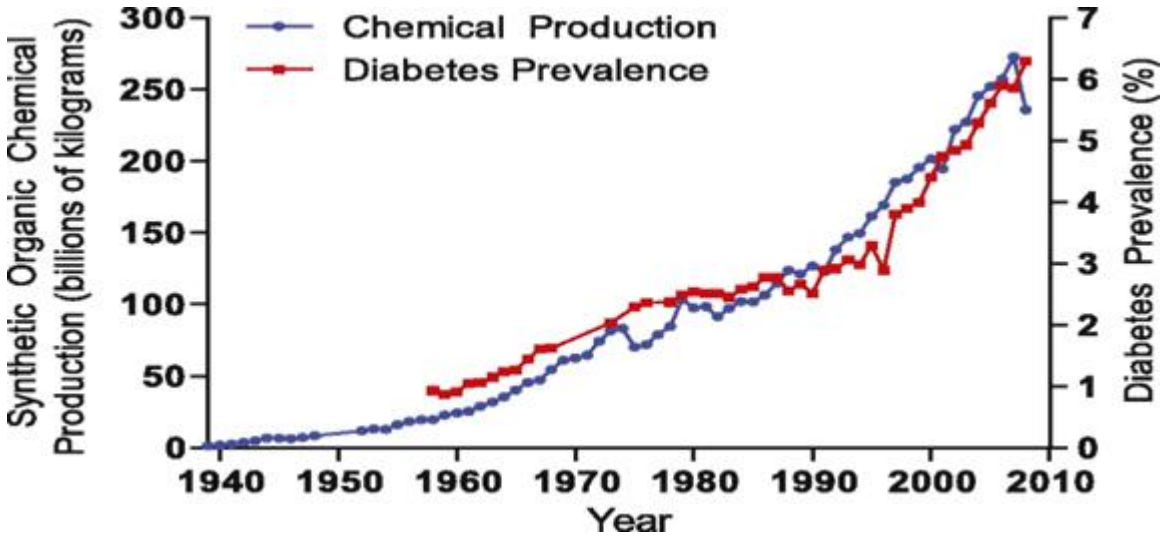
With regard to incidence, around 5% of diabetics suffer from type 1 DM and the remaining 95% suffer from type 2 DM. NIDDM is mainly due to hereditary factors, worthy lifestyles and obesity (Kumar and Clark, 2002).

According to the International Diabetes Federation (IDF) survey in 2013, the number of people living with diabetes are 282 million which increases in 2014 i.e. 387 million people it accounting for 8.2% of adults between 20 and 79 age groups.

All types of diabetes are increasing at a very rapid rate mainly type 2 diabetes. WHO 2016 data accounts for 422 million people while one year before i.e. in 2015 IDF reported 415 million diabetic patients i.e. 1 out of 11 adults are suffering from diabetes. The number of diabetes people will increase to 439 million people in 2030 which increases to 452 million sufferers in 2035 and around 642 in 2040. This depicts that 1 out of 10 adults are diabetic. (World Health Organization 2016). (International Diabetes Federation 2015; Ali *et al.,* 2017 The discouragement and the death rate in many countries around the world are due to diabetes mellitus. According to the IDF 2015 and WHO 2016 survey, about 80% of diabetes suffering people are on and below income level, so it leads to 5 million mortality in 2013 and near about 5 million in 2015 also.

According to a survey it has been recorded that of all global health expenditures 12% of expenditure is on diabetes treatment only. Many countries spent 5 to 20% of total health expenditure on one disease i.e. Diabetes mellitus International Diabetes Federation 2015; Williams 2016). Up to which the business of sale of diabetes drugs is very much i.e $35.6 billion in 2012 (Vision gain 2013), which in turn became 51.1 billion in 2015 (Global Market Insight, Inc. 2016), and it is approximately reached up to 55.3 billion in 2017 (Visiongain 2013) and 116.1 billion in 2023 (Global Market Insight, Inc. 2016). For the treatment of Type 1 type of diabetes only insulin or synthetic insulin analogues can be used(Freeland and Farber 2016; Zaykov et al. 2016), but the treatment of type 2 diabetes requires insulin or oral drugs, single API or a combination of both of them can be used. (Freeland and Farber 2015; Kokil et al. 2015; Gaitonde et al. 2016).

Between 2001 and 2009 type 2 diabetes increased by approximately 30% among youths in the U.S.(Dabelea et al. 2014). In 2011-12, type 2 diabetes is recorded in 12-14% of adults. The prevalence of type 2 diabetes is recorded more in Black than white people. The occurrence of diabetes is increasing day by day at a rapid speed. It has been reported that in every 5 teenagers 1 is suffering from high blood glucose levels i.e. hyperglycemia, which means the prevalence of diabetes increases from teenagers to adults and to the old stage. (Menke et al. 2016). From 2002-2012 type 2 diabetes is increasing with a speed of 4.8% per year in children as compared to type 1 diabetes. It is recorded more in minority class groups. (Mayer-Davis et al. 2017)



Source:https://openi.nlm.nih.gov/detailedresult.Php?img=PMC3121438_1838fig2&req=4

The study of plants for the sake of hypoglycemic, antioxidant and hypolipidemic effects give birth to a new pharmacological study for the treatment of diabetes mellitus. (Hooft, 2003). A combination of many medicinal traditional plants has been used for curing diabetes all over the world. Throughout the world, mainly in poor countries, the known ethnomedicinal plants are the only way to use the treatment of diabetic patients. According to a report, there are about 1200 species of traditional medicinal plants recorded which are used as a medicine against diabetes. Even some of them have never undergone scientific investigation, testing, and evaluation. (Marles and Farnsworth, 1995).

There are many literature reviews of herbal plants as an antidiabetic potential by many authors. (Ernst, 1997; Alarcon-Aguilera *et al*., 1998; Grover *et al*., 2002; Tiwari and Madhusudana, 2002; Bnouham *et al*., 2006).

There are so many studies of ethnomedicinal traditional plants, Polyhedral formulation of three or more medicinal plants has an anti-diabetic effect. Many medicinal plants had been used for the treatment of diabetes and obesity like Tinospora spp., Artemisia Spp, Zingiber spp., etc and also positive results have been finding out. The present work also includes the treatment of

diabetes but the difference is that in it we can take the mixture of oils of three plant seeds i.e. hemp, corn and pumpkin seeds. These all contain a protein called Glucose-dependent insulinotropic polypeptide (GIP) which activates the production of insulin hence glucose is changed into energy and the risk of diabetes became less. This is a new approach toward control over diabetes.

There are two types of hormones which are released postprandial and secreted in the intestinal epithelium to enter endocrine cells. These are secreted in the gut also called gut hormones. These are:

i.) Glucose-dependent insulinotropic polypeptide(GIP

ii.) Glucagon-like peptide (GLP 1)

These both gut hormones circulate in the body and act as markers of food consumption, which make the body active against the food intake-derived elevations of blood nutrient concentrations. These hormones are the best control of blood glucose concentration by the secretion of β cells by GIP and L cells by GLP1 by the costimulation of the pancreas approximately which doubles the amount of insulin released in response which in turn leads to the control of diabetes.

Both GIP and GLP also knew to be incretins hormones because these show the incretin effect. These both increase the postprandial increase of insulin by its secretion by stimulating the pancreas. GLP 1 is degraded by dipeptidyl peptidase 4 (DPP4) which helps in the treatment of type 2 diabetes and is hence preserved for the treatment of type 2 diabetes due to its insulinotropic effects.

Studies show that both the incretin hormones GIP and GLP 1 have insulinotropic properties but the difference lies in the activity and plasma profiles.

Table 1: Differences between GIP and GLP 1

GIP	GLP 1
It is an incretin hormone secreted by enteroendocrine K cells of the Pancreas	It is also an incretin hormone but is secreted by the L cells of the pancreas.
GIP stimulates glucagon secretion from pancreatic α cells	GLP 1 inhibits α cell activity
GIP seems to have no effect on food intake.	GLP1 has anorexigenic properties on food intake.

The incretin effect of GIP seems to be flawed in patients suffering from type 2 diabetes, it is noted that stimulation of GLP1 and inhibition of GIP secretion prove to be a curative objective in overweight patients with type 2 diabetes. The present study will focus on the

working nature to enter endocrine cells secreting these incretin hormones, the GIP-expressing K cells and the proglucagon/GLP 1-expressing L cells.

The gene structure variation suggests that during early mammalian evolution GIP undergoes expeditious sequence alteration which shows differences in the biological activity of the hormone amongst all the species. With more emphasis on it, a study shows that enzymatic processing of the pro-GIP hormone in the gut may yield significant levels of a bioactive shorter version of GIP, GIP (1–30) amide, the full biological significance of which remains to be explained. Further, it has been proposed that GIP is revealed and secreted by alpha cells of the pancreas which promotes insulin secretion.

Pathophysiological implications

There are a number of stages of disease for which GIP secretion, biological action, or receptor expression are postulated to be involved in the aetiology, an aberrant GIP-R expression is possibly involved in certain forms of food-dependent Cushing‟s syndrome. However, to date, the major focus of the path physiological implications of GIP relate to effects on type 2 diabetes, obesity, bone disorders, and brain function. GIP is also called a multifunctional and multidirectional hormone. It’s efficient in curing the diseases which are interrelated to diabetes and the diseases which arise as the result of the onset of type 2 diabetes. Hence, no doubt to name this GIP one incretin hormone is a treatment remedy for all the diseases which invade and affect the body by the onset of one single disease.

GIP and Diabetes

GIP, as an incretin hormone, is secreted rapidly from the gut into the bloodstream after nutrient absorption and makes an inherently important contribution to postprandial blood glucose control. This invention effect is estimated to account for up to 70% of the total insulin secreted after oral nutrient absorption in normal human subjects. However, the incretin effect is markedly diminished in patients with type 2 diabetes, being less than half that observed in subjects with normal glucose tolerance. Generally, the reduced incretin effect in type 2 diabetes is attributed to defective GIP action and reduced GLP-1 secretion. However, in addition to effects on pancreatic beta-cells, GIP also possesses glucose-lowering extrapancreatic effects. These include inhibition of hepatic glucose production, promotion of glucose uptake in isolated muscle, an increase of fatty acid synthesis, simulation of lipoprotein lipase activity, and reduction of hepatic insulin extraction. The cause of the reported GIP insulin-releasing ineffectiveness in type 2 diabetes is largely unknown but could include reduced GIP-R expression, down-regulation of a receptor, altered processing of GIP, defective intracellular signalling processes, or mutations of the receptor or protein.

GIP and obesity

GIP levels are increased in obesity and consumption of a high-fat diet induces K-cell hyperplasia and increased GIP protein expression. Indeed, a lipid storage action for GIP is in line with its general anabolic characteristics. There are now numerous studies linking GIP to the development of obesity resulting from chronic overconsumption of energy-rich food. In keeping with this, activation of GIP-Rs on adipocytes after feeding results in efficient storage of fat. Thus, when GIP-R signalling is annulled in animal models of obesity diabetes, the blockade of lipid metabolism and fat deposition encourages the use of circulating fat as the primary energy substrate. This results in decreased weight gain and improved insulin sensitivity and considerably outweighs the potential negative impact of the loss of the insulin-releasing GIP component of the enter insular axis. Moreover, as previously stated, the insulin tropic activity of GIP is already compromised in patients with type-2 diabetes

Other similar methodologies to inhibit GIP-R signallings such as active GIP immunization, administration of small molecular weight GIP-R antagonists, specific K-cell destruction, and dietary modification to reduce GIP secretion all result in strikingly similar metabolic effects. No serious adverse effects were observed in any of the animal studies using GIP-R signaling knockdown methodologies today.

GIP and brain

The widespread expression of GIP throughout the brain would suggest an important role for this hormone in the modulation of brain function. As such, in animal models, it has been shown that GIP induces the proliferation of adult-derived hippocampal progenitor cells. In keeping with this, mice that have a genetic knockout of the GIP-R or overexpression of GIP peptide display characteristic detrimental and beneficial effects on cognitive function; respectively. Thus, long-acting GIP-R agonists may have additional therapeutic utility for neurodegenerative diseases such as Alzheimer‟s. Moreover, a long-acting GIP-R agonist has already been shown to possess direct modulating effects on synaptic transmission and enhance the induction of long-term potentiation in mice, a key physiological marker of memory processes. GLP-1 also appears to have similar effects in the hippocampus of animal models. As with the effects of GIP analogues on diabetes, obesity, and bone, extrapolation of these findings to the human setting is still required.

Summary of pathological implications of GIP

GIP-R agonists are suggested as potential therapeutic options for type 2 diabetes, bone disorders and neurodegenerative diseases of the brain. Besides this, research now suggests that GIP-R antagonists may afford an entirely new drug class for the alleviation of obesity. Thus, modulation of GIP signalling offers an array of path physiological targets that warrant consideration as future therapeutics. However, the lack of clinical data on the biological effects

of GIP analogs, both agonists, and antagonists, makes the effectiveness, safety, and tolerability difficult to assess at present.

GIP signalling pathway

GIP is also called a gastric inhibitory polypeptide. Glucose-dependent insulin tropic polypeptide (GIP) is a chain of 42 amino acids that are produced by entering endocrine K-cells and released into the circulation in response to nutrient stimulation GIP secreted by the K-cells of the pancreas is responsible for secreting insulin during insulin deficiency GIP is secreted in a glucose-dependent manner due to which it is also called as incretins. Mammalian GIP structure is well defined and the biological activity is maintained both by the N-terminus and central region of the molecule.

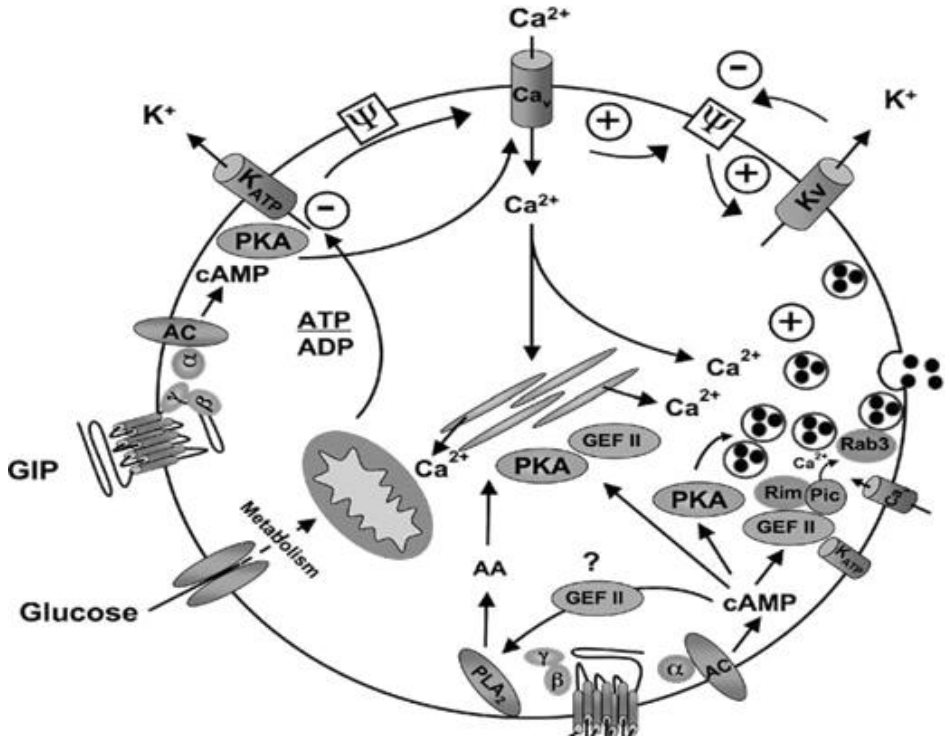


Figure 1: Representation of the main signalling pathways by which glucose and GIP are proposed to stimulate insulin secretion

Consecutively with secretion dipeptidyl peptidase IV (DPP-IV) is responsible for GIP metabolism. Keeping in view its insulin tropic activity, GIP also performs a much more valuable function in the mammalian body like growth promotion, helping in surviving the pancreatic b cell which promotes the stimulation of adipogenesis. The brain, cardiovascular system, bones and gastrointestinal tract also get benefitted from the action of GIP. The receptor of GIP belongs to the B-family of G protein-coupled receptors which in turn results in the activation of Adenylyl cyclase (AC) and Ca2þ-independent phospholipase A_2 and also activates the protein kinase (PK) A and PKB. The Mek1/2-Erk1/2 and p38 MAP kinase signalling pathways are among the

downstream pathways involved in the regulation of b-cell function. The expression of the Bcl-2 which is anti-apoptotic can be increased by GIP which leads to decreases in the expression of pro-apoptotic Bax, which results in less b-cell death and increasing the probability of survival of b-cell leads to the production of insulin and decreasing blood glucose level and also lessen the chances of diabetes mellitus. Lipoprotein lipase activity and lipogenesis also increase when GIP interacts with insulin in the adipose tissue.

Insulin can be primarily vitalized by Glucose. When it enters the b-cell, here glucose can be metabolized by glycolysis and mitochondrial oxidation. Due to which ATP?ADP increase inside and which led to the closure of ATP-sensitive Kþ(KATP) channels, depolarization of the membrane, activates the voltage-dependent Ca2þ channels (VDCCs) and increases in intracellular Ca2þ, with insulin-granule exocytose which is again followed by membrane depolarization intervene by voltage-dependent Kþ (KV) and Ca2þ-sensitive K (KCa) channels. The gut hormones (incretin) act by potentiating membrane depolarization and intracellular Ca2þ levels increases.

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PHOSPHOLIPASE A_2 IN INFLAMMATION AND CANCER

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Currently, one of the characteristics of cancer is an inflammatory reaction in the tumour microenvironment. Locally active small molecule lipid compounds called lipid autacoids, which are produced by the body, have lately been linked to cancer. They play a crucial role in tissue homeostasis and inflammation.

Phospholipases:

Phospholipids, an important part of cell membranes, are hydrolyzed by phospholipases (PLs), a class of enzymes that is found in all living organisms. Phospholipases are widely distributed in nature and have a variety of functions, including signal transduction, the creation of lipid intermediaries and second messengers, the digestion of metabolites (humans), and several pharmacological activities in snake venom. Four kinds of PLs—PLA (PLA1 & PLA2), PLB, PLC, and PLD—are distinguished based on the location where hydrolytic split of the phospholipid is induced by the enzyme. In living organisms, phospholipases A2 (PLA2) are a common member of the PLA superfamily of enzymes. When phospholipids are present within the cell membrane, PLA2s catalyze cleavage of acyl-ester linkages by hydrolysis at the sn-2 position. Free fatty acids, primarily arachidonic acid (AA) is generated as a result of this hydrolysis. Therefore, prostaglandin H2 (PGH2), the precursor to thromboxanes and the highly inflammatory prostaglandin E2 **(**PGE2**)**, is produced when cyclooxygenase **(**COX**)** enzymes digest AA.

The isoforms of PLA2 can be divided into six major categories, including secretory PLA2, platelet-activating factor acetylhydrolase, lysosomal PLA2, Ca-independent PLA2, cytosolic PLA2 and adipose-specific PLA2. Again, each group is divided into subgroups based

on inhibiting capacity. There are many subtypes within each of groupings, according to study. (Greene et al., 2011)

The basic concept of PLA2

Arachidonic acid is converted into inflammatory eicosanoid molecules by PLA2, one of its many crucial physiological functions. A number of inflammatory conditions, such as rheumatoid arthritis, atherosclerosis, several types of cancer, cardiac disease, and many other inflammatory diseases, are influenced by these compounds. The emergence of pharmaceutical substances that act as PLA2 inhibitors is intriguing for our approach to treating different inflammatory disorders in the future. (Dennis *et al.*, 2011; Magrioti and Kokotos, 2010)

Different types of PLA2 enzymes

Secretory PLA2 (sPLA2)

The secretory PLA molecule has six disulfide bridges as well as one histidine/aspartate active site region that catalyses the reaction with calcium as a cofactor. Instead of reacting with monomers, substrate aggregation results in an increase in secretory PLA activation. This process, called interfacial aggregation, involves the combination of hydrophobic and electrostatic forces to promote the binding of secretory PLA to phospholipid membranes. The functional capacity of several aromatic amino acids, among which tryptophan is the most remarkable in function, determines the binding capacity. There are 10 main subtypes of this group, according to studies.

Many different bodily processes have been linked to secretory PLA in studies. With regard to several gram-positive and gram-negative bacteria, the enzyme has potent antibacterial and antiviral properties. This activity's mechanism involves the breakdown of membrane phospholipids, which allows for access of the cell's peptidoglycan cell wall. Chemokine receptor inhibition is a key component of secretory PLA's antiviral function since it finally stops viruses from infecting host cells. Prostanoid and leukotriene-mediated inflammation is started by secretory PLA, which is another significant activity of the substance. Arachidonic acid decomposition leads to the production of bioavailable eicosanoid molecules, which mediates this process. The role PLA may have in triggering allergy and anaphylactic events by activating mast cells and causing the release of histamine has also been the subject of research.

For a very long time, attempts have been made to synthesise inhibitors of the enzyme for the therapy of asthma as well as atherosclerosis in connection to cardiovascular disorders due to the well-known importance of secretory PLA in the development of a large spectrum of inflammatory disease processes. Broad-spectrum blockers of the secretory PLA2, like varespladib, have been demonstrated to significantly reduce the diameter of atherosclerotic tissue lesions and also raise HDL levels in mice. These findings suggest that the enzyme is still a good target against the prevention and therapy of atherosclerosis, and that additional studies are required to determine its safety and effectiveness in humans. Upstream or downstream enzymes

in the same pathway may be used as alternative research targets for the enzyme to obtain similar outcomes, such as peroxisome proliferator-activated receptors (PPAR) (Kudo and Murakami, 1999)

Cytosolic PLA2

Six members of the cytosolic PLA super group have 749 amino acids each and other structural commonalities. The majority of cytosolic PLAs are dependent on intracellular calcium-binding, which helps the enzyme work at the phospholipid membrane, for their activity. The enzyme specifically affects the sn-2 location of arachidonic acid. Micelle substrates are also acted upon by cytosolic PLA. Its impact on micelles differs from its impact on phospholipid membranes in that it does not necessitate calcium activation.

The main activities of cytosolic PLA that have been examined so far rely on an elevation in cytosolic calcium that makes it easier for the enzyme to go to intracellular phospholipid layers surrounding the nucleus. This is made possible by the enzyme's ability to bind intracellular calcium, which balances the enzyme's anionic molecules and encourages hydrophobic contact with membrane substrates. Numerous additional enzymes use the process of phosphorylation to regulate the function of cytosolic PLA after becoming attached to the phospholipid membrane. rachidonic acid hydrolysis, a crucial main activity of cytosolic PLA, facilitates the substrate metabolism in the cyclooxygenase (COX) and otherwise lipoxygenase (LOX) pathways. Eicosanoids, the resultant chemicals' physiologically active counterparts, are crucial for intracellular immunity. A significant immunologic enzyme called NADPH oxidase, which generates superoxide molecules to destroy infections, is stimulated by cytosolic PLA. The control of G1 phase advancement during the cell cycle is one of the major additional roles of cytosolic PLA.

Resistance to a number of inflammatory-mediated diseases, such as rheumatoid arthritis, and acute respiratory distress syndrome occurs from disruption in the proper functioning of cytosolic PLA2, which prevents the inflammatory response from occurring. Adenocarcinoma of the lung, estrogen-dependent breast cancer, and glioblastoma multiforme are only a few of the cancers for which research has shown that cytosolic PLA plays an important part in the pathogenesis. It is a feasible research focus for disease intervention due to the impact of the enzyme's overactivity on numerous disease processes. A diminished functioning of renal concentration was one of the negative effects seen in knockout mice without any enzymatic activity. (Leslie, 2015)

Calcium independent PLA2

Calcium independent PLA2 is different from the sPLA2 and cPLA2 as calcium is not necessary for its activation (like cytosolic and secretory PLA2). It is made up of 752 amino acids, which will control different functions as ATP adherence, and calmodulin interlink. It

enhances the cell cycle occurrence and based on the cell functions, increases cell death. Ca-independent PLA2 encourages the average production of bones, glucose-dependent insulin storage, and sperm cell maturity, regular work of smooth and skeletal muscles, also regeneration of nerves action after the injuries. Ca-independent PLA2 participates in apoptosis initiation in beta cells of pancreas, leading to the symptoms in diabetes mellitus. Calcium independent PLA2 inhibitors are having less used than other enzymes. It is used effectively with traditional chemotherapeutic agents for controlling ovarian related carcinomas.

Resistance to a number of inflammatory-mediated diseases, such as rheumatoid arthritis, and acute respiratory distress syndrome occurs from disruption in the proper functioning of cytosolic PLA2, which prevents the inflammatory response from occurring. Adenocarcinoma of the lung, estrogen-dependent breast cancer, and glioblastoma multiforme are only a few of the cancers for which research has shown that cytosolic PLA plays an important part in the pathogenesis. It is a feasible research focus for disease intervention due to the impact of the enzyme's overactivity on numerous disease processes. A diminished functioning of renal concentration was one of the negative effects seen in knockout mice without any enzymatic activity (Kudo and Murakami, 2002).

Lysosomal PLA2

Because of its well-documented distribution to lysosomes within cells, lysosomal PLA gets its name. It is capable of acting as a phospholipase (acyl-transferase) and show preference for the ligands phosphatidylethanolamine (PE) as well as phosphatidylcholine (PC) inside lysosomes. Its phospholipase activity is attributable to the catalytic amino acid triad constituted of aspartic acid, histidine, and serine. Without interacting with calcium directly, the enzyme can work independently. The presence of calcium, though, can change its function because it interacts with other downstream or upstream molecules that control it.

The breakdown of phospholipids inside lysosomes is significantly aided by lysosomal PLA. Most importantly, it has a role in the breakdown of surfactant phospholipids and is highly expressed in alveolar macrophages. This procedure stops the buildup of phospholipids inside of cells. Phospholipidosis is caused by improper enzymatic activity and manifests as splenomegaly and enhanced foam cell production in knockout mice. Through the preparation of lipid antigens for use by CD1 receptors in the presentation of leukocytes, lysosomal PLA also contributes significantly to immunology. This aspect has been researched in relation to pulmonary tuberculosis infection. Adaptive Th1 T-cell immune response against M. tuberculosis is formed, according to the results, in large part because to lysosomal PLA.

Despite not having received the same amount of research as other phospholipases, there is evidence that lysosomal PLA dysfunction contributes to atherogenesis and the development of phospholipidosis. From an immunologic standpoint, pulmonary T-cell activation fails due to

compromised enzymatic performance. In pulmonary tuberculosis infection, this function has been the focus of research in animals lacking in the enzyme, which displayed higher mycobacterial numbers and a diminished inflammation to infection. (Fisher, 2018)

Adipose-specific PLA2

Adipose-specific PLA has calcium-independent action toward PE and PC, just like lysosomal PLA. It does not, however, exhibit acyltransferase activity. Increased adipose-specific PLA activity causes the release of arachidonic acid, which functions as a precursor to prostaglandin E and lowers intracellular cAMP levels as well as lipolysis. Through the control of intracellular cAMP, higher enzymatic activity ultimately results in more adiposity.

Despite being referred to as an adipose-specific PLA, this enzyme is expressed at varying amounts in many tissues, with adipocytes expressing it the most. The enzyme is a suitable target for additional obesity research due to its functions in the control of lipolysis and lipid oxidation that are currently being researched. Adipocyte fatty acid oxidation and lipolysis are both increased in knock-out animals lacking adipose-specific PLA. These findings imply that the treatment of obesity may benefit from the pharmaceutical suppression of normal enzymatic function. (Wolf, 2009)

PLA2 and inflammation

PLA2 work individually on inflammation-related conditions like sepsis, arthritis, asthma and Adult Respiratory Distress Syndrome (ARDS). For people with arthritis, the specific catalytic activity of PLA2 is seen in lubricating fluid stored by the membrane lining joints and tendon sheaths. At this site, the frequently found enzyme is G-II of sPLA2. Swelling in rheumatoid arthritis is the indication of elevation in the action of PLA2 (JJ, 1989). An inadequate amount of G II and G V groups of sPLA2 in mice shows the low intensity of arthritis. In some animals, the GIIA of sPLA2 enhances the swelling activity in autoimmune arthritis and is controlled by GV of sPLA2. GIV of sPLA2 participates in the production of eicosanoids used to treat many varieties of redness. The mice lacked in GIV of cPLA2 pertinent to arthritis produced by connective tissue. A low level of GX sPLA2 leads to less production of eicosanoids. In the colorectal problem of Crohn's disease and inflammatory bowel disease, GIIA of sPLA2 levels is more. In sclerotic patients, the PLA2 level and its activity are below average. sPLA2 levels will increase in proinflammatory and conditions but having low levels in pancreatic infections (Groeneveld *et al.*, 1997). GII sPLA2 gene is made inactive to reduce the effect of pancreatitis. More activeness or increase in the number of sPLA2 cause acute respiratory distress syndrome (ARDS) (Tsao *et al.*, 2003). Recombinant mice with the gene GV sPLA2 can efficiently control surface phospholipids, which cause lung infection. The

recombinant mice lack GIIA and GX sPLA2 genes. GIIA, GV and GX sPLA2 can efficiently manage and treat ARDS infection.

The recombinant gene of GX and the high appearance of GIIA of sPLA2 easily control the broncho-alveolar and asthma infections (Triggiani *et al.,* 2009). By removing the GV, the PLA2 gene reduces pulmonary disease and minimize the hyper-responsiveness of the airways. With another inflammatory arbitrator, sPLA2s synthesize mast cells when IgE is produced in response to a perceived threat. From the macrophages of lung cPLA2, glucuronidase and mediators of inflammation sPLA2 is released from neutrophils, elastase was formed (Galli and Tsai, 2012). Another inflammatory infection is atherosclerosis, it is controlled efficiently by GIIA, GV andGX of sPLA2. With the increase in the appearance of GIIA, PLA2 leads to a rise in atherosclerotic lesions in recombinant mice. An essential function of GVIIA PLA2 (also known as Lp-PLA2) is increasing levels of atherosclerosis leading to heart-related problems. Lentiviral mediated RNAi can control efficiently Lp-PLA2, which regulates inflammation and atherosclerosis efficiently. Hence, Lp-PLA2 treats patients with heart-related issues and atherosclerotic diseases (Steen and O'Donoghue, 2013).

PLA2 and cancer

PLA2s can efficiently control cancer originating cells. In the sPLA2 (GIIA, GIII and GX) and cPLA2 (GIVA) can control the tumors and inflammations. These two types of PLA2s are more in the tumors of cancers. GIIA sPLA2 enzymes were more in quantity in the patients with epithelial cancer, adenocarcinoma and breast cancer (Matsuda *et al.,* 1991). The moving cancer cells have more GII PLA2 and mRNA levels. We can see the PLA2 part in the growth of breast cancer cells (Yamashita et al., 1994). Lung cancer cell growth was controlled efficiently by GII sPLA2. GI PLA2 cells activate MAP kinases to increase the number of pancreatic cancer cells. sPLA2 cells are more in number in stem cells of lung cancer and colon cancer rather than in healthy cells. If the sPLA2 cell number is decreased, then the occurrence of lung cancer and colon cancer can be controlled (Buhmeida *et al.,* 2009). GIIA sPLA2 have different roles in humans. The increase in their number may lead to tumor occurrence in lung, breast and prostate cells. Their decreased number could control the intestinal and gastric tumor formation (Fijneman et al., 2009). The recombinant gene of GIVA of PLA2 encourages tumor formation in the lungs, pancreas, prostate, brain, breast, and colons leading to cancers (A. Linkous *et al.,* 2009). GIVA cPLA2 occurrence was more in lung cancer cells of A549 and H460. When GIV cPLA2 number is less, it controls the urethane-induced lung cancer cells; glioblastoma tumor formation reduces colon tumors (Ilsley *et al.,* 2005). When GIVA cPLA2s were less, growth was not seen for Lewis Lung Carcinoma (LLC). Themacrophages present around the tumor take up

the role of cPLA2 in lung tumorigenesis. GIVA cPLA2 was lacking endothelial cells that are imperfect in shifting and cannot produce a vascular system in mice (Linkous *et al.*, 2010).

GIVA cPLA2 participates in causing tumorigenesis, metastasis, extensive migration, angiogenesis and isefficiently used to produce the anti-carcinoma drug. GVI calcium-independent PLA2 (iPLA2) plays an essential enzyme in spreading the tumor to a new place in the body (McHowat *et al.*, 2011). The iPLA2 cannot change tumor growth, but these were present in mice's breast cancer cells than in normal mice. Apart from this activity, this enzyme is used for the long life of the cell. There is no activity of carcinogenesis of lysosomal PLA2, but it plays an active role in phospholipid metabolism. Another type of PLA2, adipose-specific PLA2 of GXVI, acts as a suppressor of the tumor.

Natural products act as an inhibitor of PLA2 as anti-inflammatory and anticancer agents

Many natural substances that have been obtained from a variety of natural sources, including as plants, microbes, and marine-associated creatures, have been recognized as PLA2 inhibitors and working as anti-inflammatory as well as anticancer medicines. There are several secondary metabolites in this group, including tannins, alkaloids, flavonoids, and terpenoids, which have all been documented to be PLA2 inhibitors.

Rutin controls GII sPLA2s activity, acts as an anti-inflammatory agent and it is present in several plants as a glycoside (Lindahl and Tagesson, 1997). Flavanone and its other forms can efficiently control inflammation and cancer-causing cells. The secondary metabolite, coumestans extracted from the plant *Ecliptaalba*, efficiently control the PLA2 enzyme (Diogo *et al.*, 2009). Morello flavone, a flavonoid, controls sPLA2 enzymes and inflammations too. Morello flavone acts as an anti-inflammatory and as an antioxidant to control oral inflammations (Gil *et al.*, 1997). Natural flavonoid Silibinin isolated from *Silybum marianum* acts as an inhibitor of GIIA sPLA2. It controls inflammations, as well as cancer. Silibinin, acts efficiently as an anticancer agent in inhibiting MDA-MB 468 and MCF-7 human breast cancer cells. It acts on estrogen-dependent and estrogen-independent cancer cells in humans (Tyagi *et al.*, 2004). Ellagic acid obtained from *Casearia sylvestris* efficiently acts as a controlling agent for PLA2, an anti-carcinogenic and anti-inflammatory agent (Da Silva *et al.*, 2008). From *Aristolochia* species, an alkaloid extracted as aristolochic acid, which controls PLA2 efficiently. It controls snake venom PLA2 and changes to secondary structure, which is not harmful to the organism. Aristolochic acid is not medically useful due to its toxic nature. But it controls inflammations and cancer tendencies too (Chandra *et al.*, 2002; Mariappan, 2012). Piperine is an alkaloid extracted from *Piper longum* and *Piper nigrum*. It acts as a good anti-inflammatory agent and controls the arachidonic acid pathway. Even it controls many types of sPLA2s and cPLA2 *(Sastry Yarla et*

al., 2016). Piperine shows anti-inflammatory, anti- carcinogenic nature. Along with controlling PLA2s, it can efficiently control theaccumulation of blood platelets.

A terpenoid extracted from the marine sponge called "manoalide" acts as anti-inflammatory, anti-tumorigenic agent and efficiently controls PLA2 action (Dorandeu et al., 2002). One of the metabolites obtained from marine organisms is Scalaradial, which efficiently controls PLA2 activity, which in turn controls inflammation. From citrus plants, a flavanone is isolated named Hesperidin. It controls PLA_2 efficiently and as a result, controls inflammations. Hesperidin also acts as anti-carcinogenic agent (Al-Ashaal and El-Sheltawy, 2011). Rosmarinic acid acts against snake venom PLA2 controller. It is obtained from Cordia, Verbenaceae. Rosmarinic acid efficiently controls inflammation on epidermal cells and cancerous cells (Ticli *et al.,* 2005).

Pharmaceutical companies and research organisations have discovered a number of natural and synthetic PLA2s inhibitors, and some of these are indeed under clinical trials for a variety of disorders. As none of the PLA2s inhibitory molecules have yet received approval from the US Food and Drug Administration, the majority of PLA2s inhibitors continued to fail in clinical studies due to ineffectiveness and side effects. For their therapeutic uses in the prevention and therapy of inflammation and cancer related illnesses, it is therefore desirable to develop new PLA2 inhibitors or to optimise existing PLA2 inhibitory drugs with greater potency, safety, and selectivity.

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THE EFFECTS OF LOCUS OF CONTROL ON JOB SATISFACTION AND STRESS AT WORK. A STUDY ON EMPLOYEES IN THE PRIVATE SECTOR

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Abstract:

The purpose of the current research was to better understand how locus of control affects job satisfaction and stress at work. Participants were chosen on purpose to gather data. 65 responders in all were chosen. The American Institute of Stress's workplace stress survey, Paul E. Spector's work locus of control scale, and the job satisfaction survey were all employed in the research. The results show that there was no statistically significant gender difference in work locus of control, job satisfaction, or workplace stress. It was found that individuals with an internallocus of control are more likely to have higher job satisfaction. The data were analyzed using mean, S.D, Independent t-test, and Pearson's correlation coefficient. Results also showed that worklocus of control and workplace stress was found positively correlated; work locus of control and job satisfaction were found negatively correlated; workplace stress and job satisfaction were negatively correlated.

Keywords: Work Locus of control, Workplace Stress, Job Satisfaction. Private Sector employees.

Introduction:

Stress at work has been the headline of news stories and the talk of the day these days. It is a global phenomenon of contemporary lifestyles that our island is no exception. Various studies show that intense job stress can harm workers' mental and physical health, which eventually leads to lower productivity, less job satisfaction, and fewer healthy employees. It is not possible to ignore the work stress within the company. A study conducted by Anderson shows that stress occurs in any organization high or low, which in turn affects the overall job performance of the employees. For example, Pickering (2001) notes that the effects of stress in the workplace can be very varied and along with poor results, including elevated illness, absence, and staff turnover. Moreover, tension has frequently been related to industrialsabotage.

Workers often produce mechanical failures on the assembly line to break the monotony and tension of their job. Job stress influences individual productivity as well. Rose states in her study that an elevated average level of stress is to be found in every company and at every level of management and staff, which mainly affects the work satisfaction of employees. Employees who do not like their jobs can experience negative physical and mental health issues, according

to Spector. As the latter is an indicator of low employee job satisfaction, each business would like to have a minimum rate of employee absenteeism. Hellriegel *et al.* (1989) note that absenteeism is related to the degree of work satisfaction. French (2003) states in his study that the high turnover rate of employees is caused by employee discontent with their workplace. Analysis conducted by Steel and Ovalle (1984) showed that the relationship between work satisfaction and turnover is moderate,which suggests that less satisfied workers are more likely to leave their jobs. Locke (1976) equates job satisfaction with staff morale. He states that workers with higher job satisfaction think that in the long run the company will be happy, care about the quality of their job, are more loyal to the organization, have higher retention rates, and are more productive.

Job satisfaction can be defined as a happy or optimistic emotional state that results from the assessment of one's work or work experiences. This positive feeling stems from the understanding of one's work as fulfilling or enabling one's significant job values to be met, provided that these values are consistent with one's needs. Provide that values apply to what one wishes or tries to accomplish in a job. Hoppok and Spielgler describes job satisfaction as the interconnected collection of psychological, physiological, and environmental circumstances that enable workers to admit that they are happy with their employment. Besides, the role of employees in the workplace is emphasized as there is an effect of different elements on an employee within the organization.

Clark (1997) argues that if the employees are not content with the role assigned to them, they are not certain concerning factors such as their rights, working conditions are not safe, colleagues are not cooperative, not being valued by managers, and are not taken into account in the decision-making process, resulting in them feeling separate from the organization. Julian Rotter originated the Locus of Control theory in 1954. It calls people's propensity to think that power exists within them internally, with others, or the situation externally. People with an internal locus of influence assume that their initiative and ability are the product of the consequences of their actions. They think that hard work and personal skills would contribute to good results.

People with an external locus of control, on the other hand, believe that their actions do not affect future results and that the results of their actions depend on factors outside their control (Landy and Conte, 2004; Martin *et al,* 2005). Findings from the research show that an internal control locus is correlated with job satisfaction and an external control locus with job dissatisfaction. Internals who attribute performance to events under their control experience more job satisfaction than people who think they have no control over events that determine their performance. Most of the elements determine the satisfaction of employees, except for

opportunities to express one's ability, recognition, and variety of tasks. Regardless of the nature of the work, interns tend to have higher job satisfaction due to the way they perceive them.

Research questions:

a. Does work locus of control affect job satisfaction?
b. Does work locus of control affect workplace stress?
c. Does work stress affect job satisfaction?
d. Do males and females have different locus of control, work stress, and jobsatisfaction?

To answer the above research question, the following objectives have been developed in achievable terms.

Objectives:

a. To study and compare workplace stress, job satisfaction, and work locus of control on private-sector employees.
b. To study and compare workplace stress, job satisfaction, and locus of control on male and female employees
c. To study the correlation between workplace stress, job satisfaction, and work locus of control on private-sector employees.

To achieve the above objectives, the following hypotheses are generated to be tested.

Hypotheses:

H1: There is no significant difference between males and females concerningtheir workplace stress, job satisfaction, and work locus of control.

H2: There is no significant correlation between workplace stress, job satisfaction, and work locus of control

H3: There is no significant relationship between locus of control and jobsatisfaction.

Methodology:

The present study was carried out on 65 employees of private sector organizations, (34 males and 31 females) who were selected purposively. At first, participants were informed about the purpose of the study. A set of questionnaires were provided. The participants were requested to read each statement and express their feelings by putting on tick marks at the appropriate point.

Tools used:

The Job Satisfaction Survey, by Paul E. Spector (JSS), is a 36-item, nine-facet scale to assessemployee attitudes about the job and aspects of the job. A summated rating scale format is used, with six choices per item ranging from "strongly disagree" to "strongly agree."

The Work Locus of Control Scale by Paul E. Spector (WLCS) is a 16-item instrument designed to assess control beliefs in the workplace, that is, whether a person believes he or she can control events at work or whether control resides in others. The format is summated rating

with six response choices: disagree very much, disagree moderately, disagree slightly, agree slightly, agree moderately, agree very much, scored from 1 to 6, respectively.

The Workplace Stress Survey by The American Institute of Stress is a 10-item scale designed to assess work-related stress. The format is summated rating with three response choices: you strongly disagree, agree somewhat, strongly agree.

Research variables

The present research is a relational study that considered the principles of applied research and is based on three variables namely - work locus of control, workplace stress, and job satisfaction.

Result and Discussion:

The statistical tests used to analyze the data are Mean, S.D., independent t-test, and Pearson product-moment correlation r'. IBM SPSS was used for statistical analysis. First, Independent t-tests were conducted to evaluate H_1.

Table 1: Independent t-test results comparing males and females on work locus of control

Gender	N	Mean	SD	t	df	p
Male	34	40.94	11.086	.336	63	.369
Female	31	40.06	9.822			

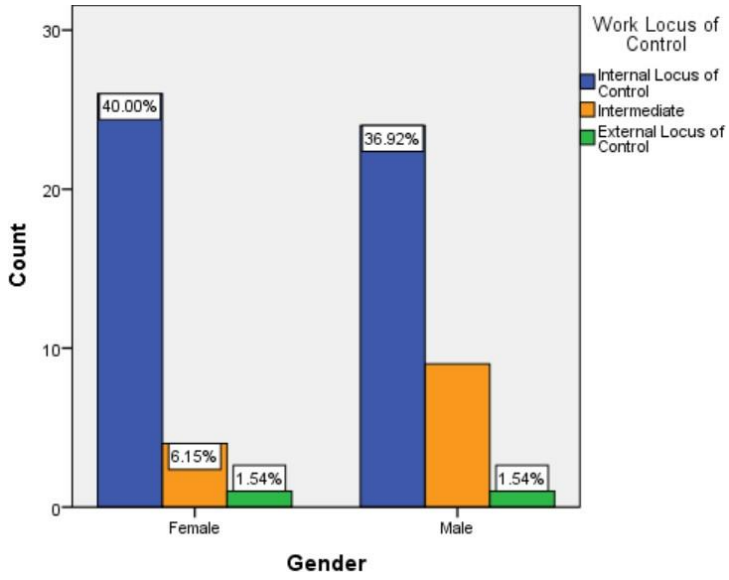

Figure1: Percentage distribution of work locus of control in female and male employees

An independent-samples t-test was conducted to compare the work locus of control in females and males (Table 1). There was no significant difference in the score for males (M = 40.94, S.D = 11.086) and female (M = 40.06, S.D = 9.822) conditions; t(63) = .336, p = .369, which is not significant at 0.05 level. This indicates that there is no significant difference between male and female employees concerning work locus of control.

Table 2: Independent t-test results comparing males and females on job satisfaction

Gender	N	Mean	SD	t	df	P
Male	34	153.15	27.467	.55	63	.478
Female	31	152.17	27.124			

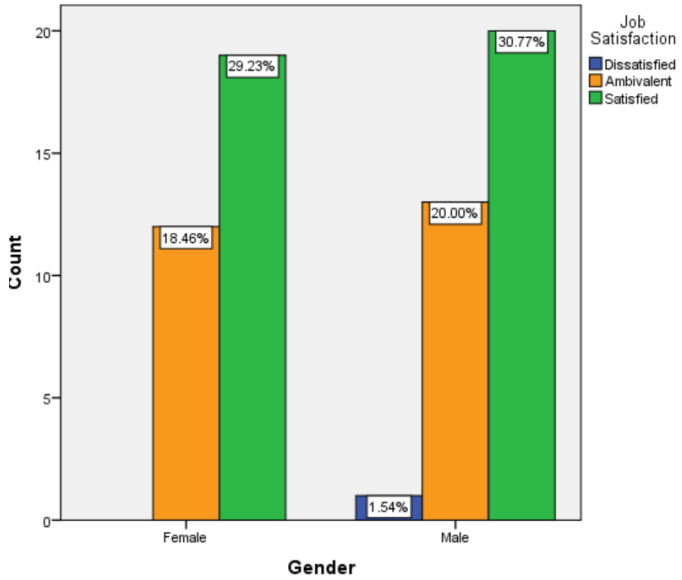

Figure 2: Percentage distribution of job satisfaction in female and male employees

An independent-sample t-test was conducted to compare job satisfaction in females and males (Table 2). There was no significant difference in the score for males (M = 153.15, S.D = 27.467) and females (M = 152.77, S.D = 27.124) conditions; t (63) = .055, p = .478, which is not significant at 0.05 level. This indicates that there is no significant difference between male and female employees regarding Job Satisfaction.

Table 3: Descriptive statistical reports of subscales in Job satisfaction

	Percentage Distribution		
	Dissatisfied	**Ambivalent**	**Satisfied**
Pay	30.8	32.3	36.9
Promotion	9.2	46.2	44.6
Supervision	6.2	18.5	75.4
Fringe Benefits	27.7	33.8	38.5
Contingent Rewards	18.5	32.3	49.2
Operating Conditions	30.8	41.5	27.7
Coworkers	3.1	20.0	76.9
Nature of Work	3.1	32.3	64.6
Communication	10.8	26.2	63.1

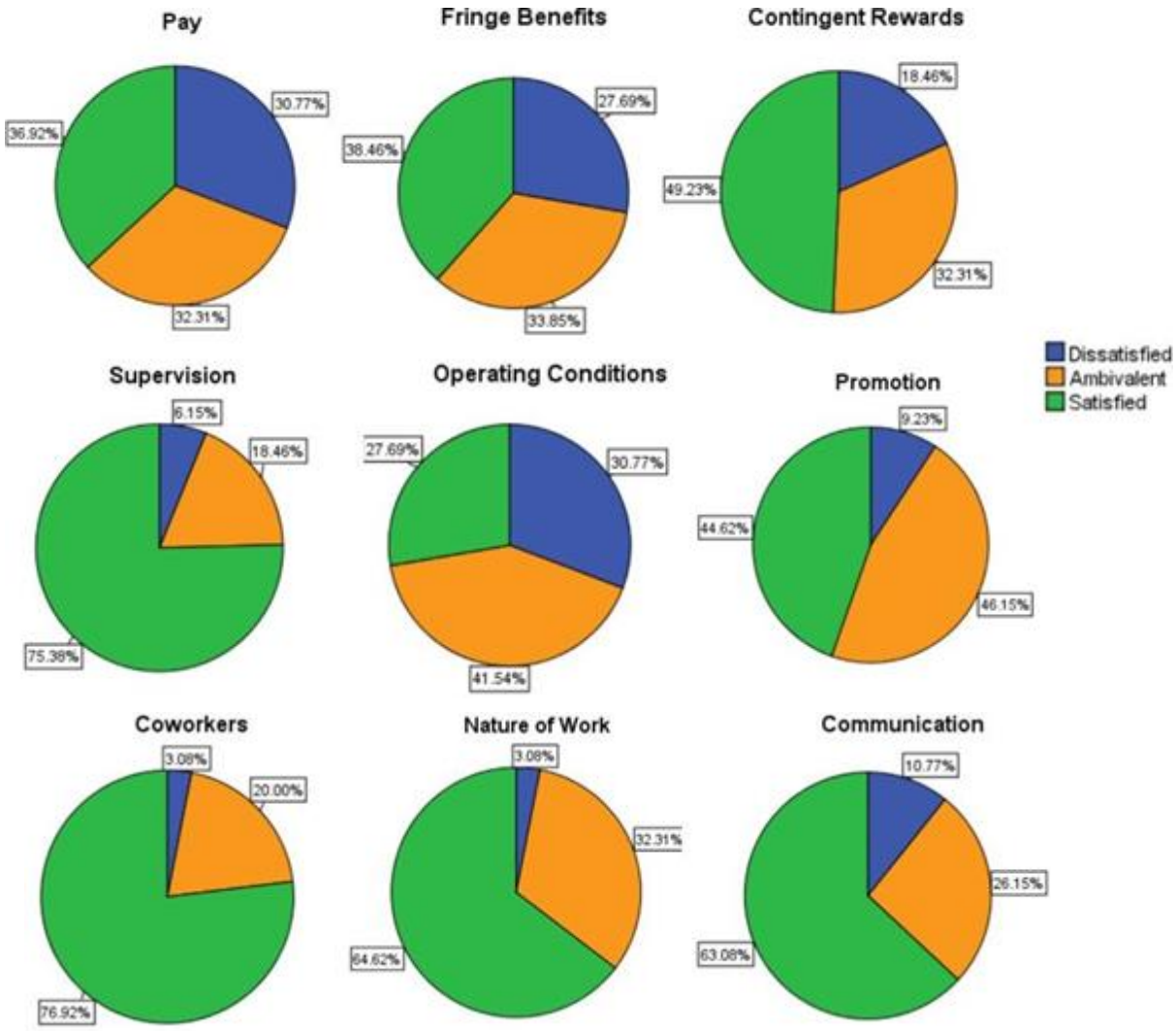

Figure 3: Percentage distribution of level of satisfaction for each subscale of job satisfaction

Table 3 and Figure 3 show the descriptive statistical analysis report and percentage distributionof different subscales of job satisfaction measured in the employees respectively. An independent- samples t-test was conducted to compare workplace stress in females and males (Table 4).

Table 4: Independent t-test results comparing males and females on workplace stress

Gender	N	Mean	SD	t	df	P
Male	34	39.06	19.204	-.159	63	.437
Female	31	39.77	16.798			

There was no significant difference in the score for male (M = 39.06, S.D = 19.204) and female (M = 39.77, S.D = 16.798) conditions; t (63) = -.159, p = .437, which is not significant at

0.05 level (Table A.4). This indicates that there is no significant difference between male and female employees with regards to workplace stress.

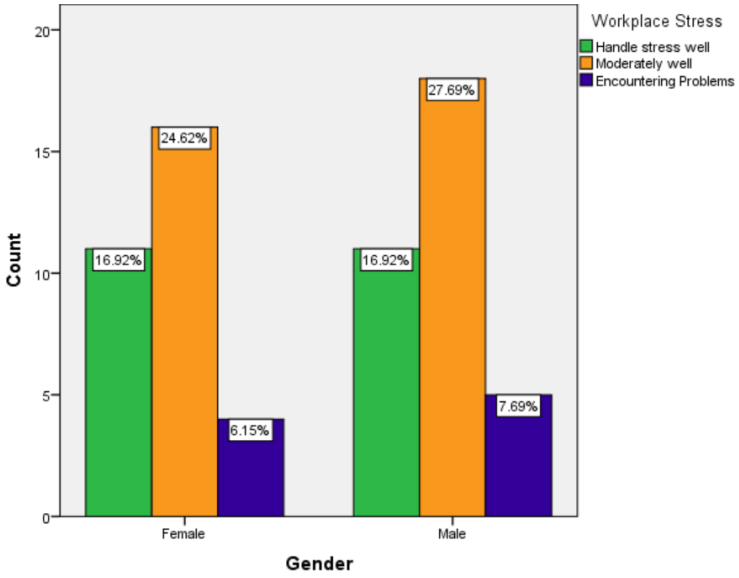

Figure 4: Percentage distribution of workplace stress in female and male employees

These results indicate that there is no significant difference between male and female employees regarding their work locus of control, job satisfaction, and workplace stress.

Correlation between the study variables – work locus of control, Job satisfaction, and Workplace stress

To measure the relationship between the variables used in the study, Pearson's *r* parametric test ofcorrelation was computed to assess the strength and direction of the relationship between the studyvariables. Pearson's test of correlation was conducted to evaluate H2.

The value of *r* in table 5 represents the statistical reports generated on computing Pearson's correlation coefficient among the variables- work locus of control, job satisfaction, and workplace stress. The correlation strength is weak if the value of *r* ranges from 0 to 0.2 and strong if the values range from 0.3 to 1.

Table 5: Correlation between work locus of control, job satisfaction, and workplace stress

Variables	N= 65		Correlation *r*			*p*		
	Mean	S.D	Work Locus of Control	Job Satisfaction	Workplace Stress	Work Locus of Control	Job Satisfaction	Workplace Stress
Work Locus of Control	40.52	10.430	1	-.631**	.142		.000	.259
Job Satisfaction	152.97	27.091	-.631**	1	-.151	.000		.230
Workplace Stress	39.40	17.960	.142	-.151	1	.259	.230	

**. Correlation is significant at the 0.01 level (2-tailed).

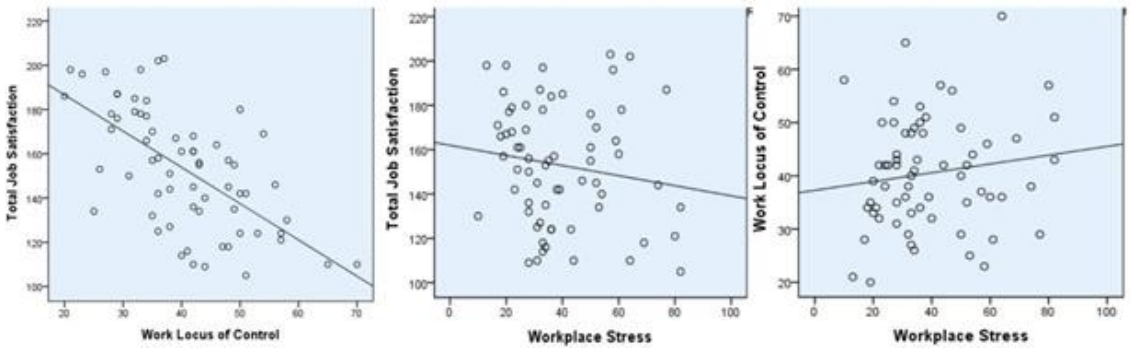

Figure 5: Pearson product-moment correlation scatter plots comparing Work locus of control, Totaljob satisfaction, and workplace stress

Table 5 shows that there was a strong negative correlation between work locus of control and job satisfaction, r = -.631, p < .001. There was a weak positive correlation between work locus ofcontrol and workplace stress, r = .142, p = .259. There was a weak negative correlation between job satisfaction and workplace stress, r = .151, p = .230. An independent t-test was conducted to evaluate H3.

Table 6: Independent t-test results comparing internal and external locus of control on Job Satisfaction

	Work Locus of Control	N	Mean	SD	t	df	P
Job Satisfaction	Internal Locus of control	50	158.52	26.250	3.231	63	.001
	External Locus of control	15	134.47	21.597			

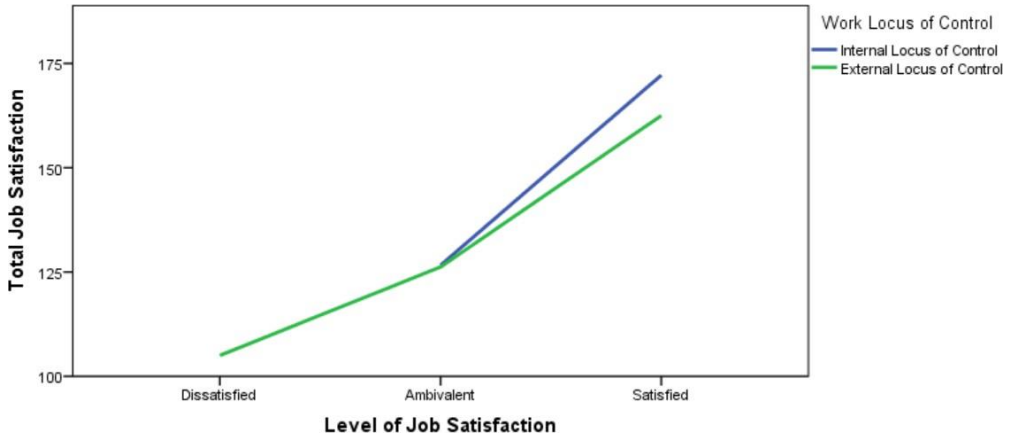

Figure 6: Level of job satisfaction in internal locus of control and external locus of control group employees

An independent-sample t-test was conducted to compare Job Satisfaction in an internal and external locus of control groups (see Table A.6). There was a significant difference in the score forthe internal locus of control (M = 158.52, S.D = 26.250) an external locus of control (M = 134.47, S.D= 21.597) conditions; t(63)= 3.231, p = .001, which is significant at 0.05 level. Figure 6 clearly shows that employees with an internal locus of control had a higher level of job

satisfaction. This indicates that there is a significant difference between work locus of control concerning Job Satisfaction (H3).

Conclusion:

In conclusion, it can be stated that work locus of control is positively correlated with workplace stress; and job satisfaction is negatively correlated with workplace stress and work locus of control.There was no significant difference in workplace stress, job satisfaction, and work locus of controlwith gender. The results indicate that employees with an internal locus of control reported higherjob satisfaction when compared to employees with an external locus of control. The present studywas conducted on employees in private-sector organizations. It can be further suggested that this study can be conducted on a larger population to establish greater generalizability of these findings.

Ethical standards:

The author asserts that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutionalguides on the care and use of laboratory animals.

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BIOMEDICAL WASTE MANAGEMENT: A STUDY ON ASSESSMENT OF COMPLIANCE RATE AMONG HEALTH CARE PROFESSIONALS IN A MULTISPECIALITY HOSPITAL

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Abstract:

Healthcare waste from hospitals, laboratories, and pharmacies should be disposed of properly to prevent significant harm to the environment and people. Several diseases may spread as a result. Regulatory organisations have pushed for more environmental controls in healthcare institutions as a response to this. The very first standard on the topic to be published in India was "Solid waste - Hospitals-Guidelines for management" by the Bureau of Indian Standards, but it had no effect on the state of affairs. The government's effort, "Biomedical waste (Management & Handling rules) 1998," is quite important in this regard. Despite the numerous efforts made, our government still has to take decisive action to force industry to create and adhere to environmental rules.

Keywords: Biomedical, Hazardous Waste, Hospitals, Health care

Introduction:

Balance between the environment and human beings is the crucial for healthy life and growth. Therefore, it is the utmost responsibility of the government to strike and maintain a balance between the two for the benefit of the mankind. (Gordon and Hardt, 2004). To fulfil this responsibility the government has enacted various laws in order to protect the environment which includes land, water and soil .It has also been sen that the economic development, social development is dependent on the environment development.So, the environment protection laws plays a very crucial role. It is the responsibility of all the sectors to safeguard the environment including health care sector (Rao and Bhatia, 2004). Hospitals, dispensaries, laboratories and other health-care facilities aim o provide the best possible health care facilities to the patient and it is their utmost duty to do so without harming the environment and to avoid improper disposal of hospital waste (Rao and Garg, 1994). In India, the first standard regarding hospital waste management was brought by the Bureau of Indian Standards which was entitled ‘Solid Wastes-Hospitals-Guidelines for Management’, however it was unable to bring any significant improvement in the situation. Later on, ‘Biomedical waste (Management and Handling) Rules, 1998’ was introduced which hold a great significance in this regard. The Biomedical Waste Management and Handling) Rules, 1998 came into power on 1998. In exercise of the forces

presented by segment 6, 8 and 25 of EP Act, 1986, the Central Govt. advised these guidelines for the administration and Handling of biomedical squanders created from Hospitals, centers, different organizations for logical administration of Biomedical Waste. The Biomedical waste methods any waste, which is created during the conclusion, treatment or vaccination of people or creatures or in look into exercises relating thereto or in the generation or testing of natural and incorporating classes referenced in plan I of the Rules. It will be the obligation of each occupier of an organization creating bio-restorative waste which incorporates an emergency clinic, nursing home, center, dispensary, veterinary foundation, creature house, neurotic research facility, blood donation center to find a way to guarantee that such waste is taken care of with no negative impact to human wellbeing and the earth. The environment.Biomedical waste includes bundling, unused gauzes, mixture units, and so on. Biomedical wastelike blood stained gauze if disposed off improperly can cause damage to the environment and contaminated diseases in human beings. As definite beneath, disposed of sharps are viewed as biomedical waste whether they are stained or not, because of the plausibility of being polluted with blood and their inclination to cause damage when not appropriately contained and discarded. Biomedical waste is a health hazard.

Biomedical waste might be solid or fluid. Instances of biomedical waste incorporate disposed of blood, sharps, stained gauze and dressings, recognizable body parts (counting those because of removal), other human or creature tissue, utilized wraps and dressings, disposed of gloves, other medical supplies that may have been in contact with blood and body liquids, and other hospital waste that shows the qualities depicted previously. Biomedical waste is generated from organic and medicinal sources and exercises, for example, the analysis, avoidance, or treatment of diseases. Regular generators (or makers) of biomedical waste incorporate emergency clinics, wellbeing centers, nursing homes, dispenseries, medicinal research labs, workplaces of doctors, dental specialists, and veterinarians, home human services, and mortuaries or burial service homes. In social insurance offices (i.e., emergency clinics, centers, specialist's workplaces, veterinary medical clinics and clinical labs), waste so generated may on the other hand be called medicinal or clinical waste. Biomedical waste is particular from typical rubbish or general waste, and varies from different sorts of perilous waste, for example, substance, radioactive, widespread or modern waste. Health or medical centres produce hazardous dangerous synthetic compounds and radioactive materials. Removal of this waste is a natural worry, the same number of medical discarded material are named irresistible or biohazardous and might prompt the spread of irresistible ailment. The most widely recognized peril for people is the contamination which additionally influences other living beings in the district. Day by day generation to the waste (landfill) prompts collection of hurtful substances or organisms in the individual's body. It has been observed that the verall population isn't probably

going to be unfavorably influenced by biomedical waste produced in the conventional health care setting. They found, in any case, that biomedical waste from those settings may represent damage and introduction of health dangers by means of contact with medicinal waste for specialists, attendants, and janitorial, clothing. Further, there are open doors for the overall population to come into contact medicinal waste, for example, needles utilized illegally outside human services settings, or biomedical waste created through home wellbeing care.Biomedical waste must be appropriately collected and discarded to secure the earth, overall population and employees, particularlymedical staff and sanitation laborers who are in danger of coming in contact with biomedical waste as a health related risk. Steps in the administration of biomedical waste incorporate, collection, dealing with, capacity, treatment, transport and disposal.

The advancement and administration of a national waste administration approach can improve biomedical waste administration in healthcare facilities. Treatment of the medical waste especially hazardous waste may happen nearby or off-site. On location treatment of enormous amounts of biomedical waste normally requires the utilization of moderately costly gear, and is commonly just practical for huge medical clinics.

Off-site treatment and removal includes enlisting of a biomedical waste removal administration whose workers are prepared to gather and take away biomedical waste in special bins and containers.Several amendments in biomedical waste management act have been done by Government of India. Apart form this act, Government of India has enacted several other legislation to protect the environment like Air (Prevention and Control of Pollution) Act, 1981, Water (Prevention and Control of Pollution) Act 1974, Environmental Protection Act 1987 etc were introduced by Government of India (Singh and Sarma, 1996). However, along with the measures and initiatives taken by the government, cooperation from the society is also very crucial in waste management for the betterment of the environment.

Research objective:

The research main goal was to determine the compliance rate for source-based bio-medical waste segregation throughout all patient care areas within the hospital.

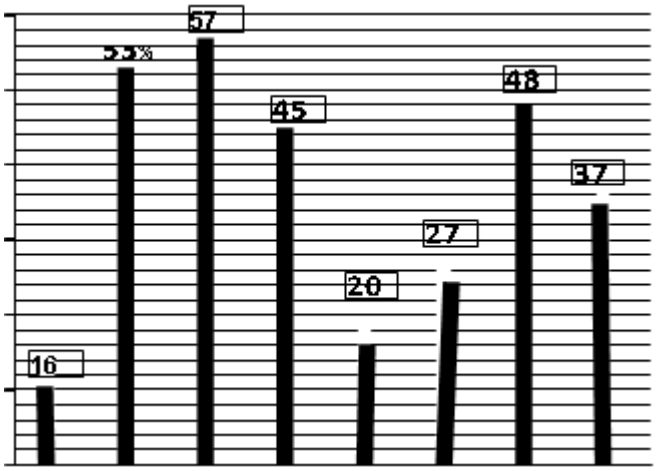
Methodology:

The research was purely observational. Methods used in this study included self-assessment of bio-medical waste (management andhandling) Rules 1998 and monitoring of bio-medical waste separation and ability to handle in the hospital. The hospital's numerous departments' waste separation procedures were extensively scrutinised. Data on the amount of mistakes made in the bin types and segregation techniques were noticed or documented. Different statistical techniques and graphical representations were used to analyse the data.

Results:

After analyzing the data, following results were obtained:

Compliance rate (Before the implementation of corrective measures)



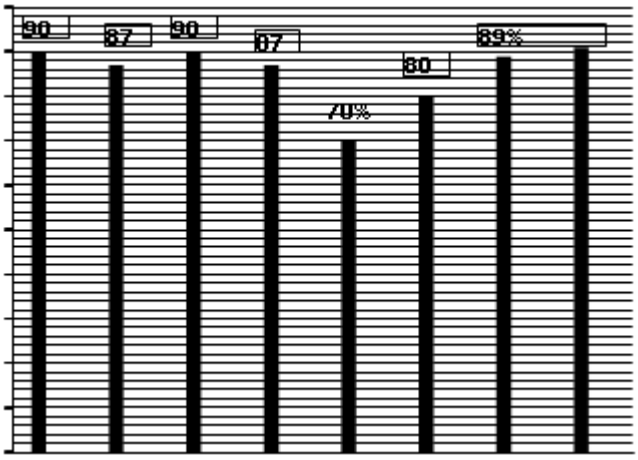
Data analysis

- I.C.U-1 has the lowest compliance rate (16%) followed by Cath Lab (20%)
- G.W-2 has the highest compliance rate of 57% followed by G.W-1 (53%)
- Compliance rate of G.W-3 is 45%
- Compliance rate of Dialysis unit is 27%
- Compliance rate of H.D.U is 48%

Measures taken

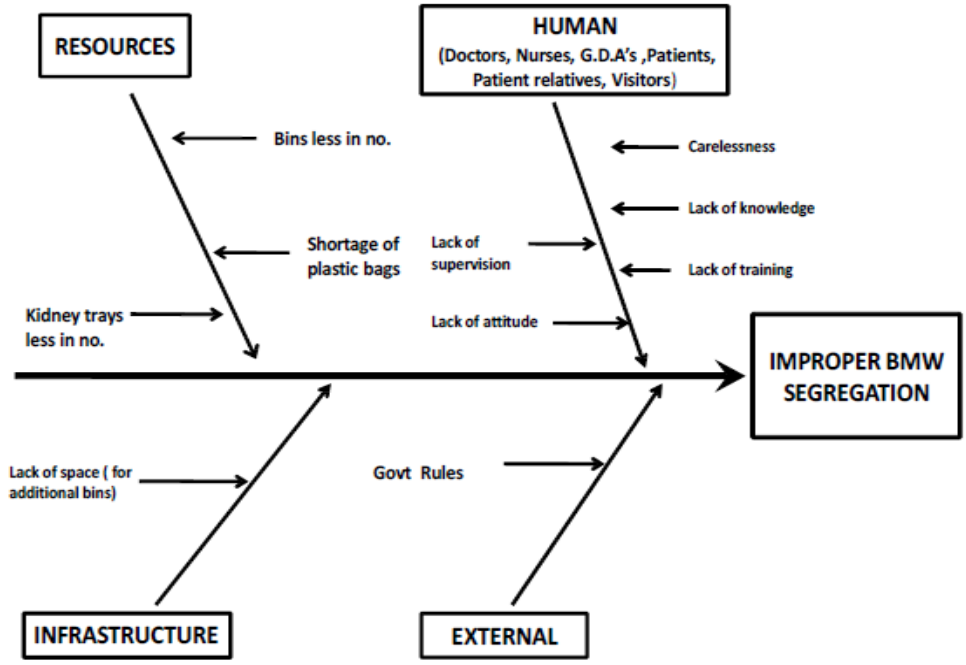
- Awareness classes were conducted by the Quality cell to educate nurses and G.D.A's regarding the importance of B.M.W Segregation at source.
- Extra bins were provided in the departments (wherever required)
- Checking/ Observation / Monitoring of the various departments

Compliance rate (After the implementation of the corrective measures)



- Lot of improvement has occurred and waste mixing has reduced to a great extent.
- I.C.U-1 and Dialysis Unit has shown maximum improvement.

Fish bone analysis



Conclusion:

From the following, it was analyzed that there is non-compliance regarding bio-medical waste segregation at source in the Hospital. All the departments under study show non-compliance of bio- medical waste.

Recommendations:

The following are the recommendations to improve the segregation at source:

1. Every week, a nurse should be given additional responsibility to see that the segregation is proper in their departments and to give the weekly report regarding the segregation to the nursing head.
2. Based on the report given, strict action like warning letter should be taken so that the non-compliance is not repeated again.
3. Covered bins should be provided in the patient care areas.to prevent spillage and the spread of infection.
4. Bio-hazard symbol should be on the hazardous waste bins will help in reducing errors
5. Proper instructions and classes to give information regarding the colour coding and different containers used for disposal should be regularly provided to the staff in order to minimize improper waste disposal

So the study shows that from the planning stage to day to day execution of a proper waste management system in the health care establishments, management aspects are of crucial importance.

Dereliction of duty and carelessness at any stage can affect the whole system Therefore, all staff should know about their precise role – what is expected of them. Hospitals can have adverse effects on nature and healthy living of an individual (patient). In this ever increasing world of pollution, it is high time that our Government takes concrete steps to insist upon industries to frame environmental policies and to be bounded by it.

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CHIMERIC PROTEINS AND THEIR APPLICATIONS IN BIOMEDICAL SCIENCES

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Abstract:

The compromised half-life, non-specificity, and requirement of multiple dosages to achieve optimum response are the limitations of natural biomolecules. Therefore, recombinant proteins have attracted the biomedical and health science researchers to explore their potential for clinical uses. But the side effect and cost are also major barriers and limit their use as therapeutics. Chimeric proteins can solve these problems and can become the magic tools for health sectors. Chimeric proteins are being investigated for various purposes like extension of half-life of effector molecules, toxicity studies, and as a part of target specific delivery systems. Many of these chimeric proteins are already in clinical targets. In this chapter the advantages and application of chimeric proteins is being explored systematically.

Keywords: Chimeric Proteins, Immunity, Therapeutics, Half-life

Introduction:

The use of recombinant proteins for the treatment of diseases is a well established phenomenon. It is seen that these recombinant proteins are superior to their natural counterparts. But many times these therapeutic proteins or peptides are unstable or have short half-lives in their native form. These efficient drugs or cytokines show poor bioavailability due to faster clearance. It is reported that many proteins having molecular mass less than 20 kDa (e.g. many cytokines and immune-proteins) are easily filtered from renal tubules and cleared from the system. Generation of chimeric proteins is a way to minimize these limitations, design new therapeutic, adjuvants and to address many diseases including cancer (Manoj *et al.*, 2017). With the help of rDNA technology, it is easy to fuse two or more genes together and obtain chimeric proteins having multiple functional properties derived from each of its components (Manoj *et al.*, 2017).

By using rDNA technology or genetic engineering, these chimeric proteins are created artificially for use in biological research particularly for therapeutics. For the construction of the chimeric proteins, the stop codon from the cDNA sequence of first protein should be removed, then add the cDNA sequence of the second protein. This fused DNA sequence will then be expressed in cells as a single protein. This chimeric proteins can be engineered to include the

full length sequence of both original proteins, or only a portion of either or full length sequence of one protein and a portion of another protein. Many times linker or spacer peptides are also used to fuse two proteins which provide flexibility if required and prevent interaction of partner proteins (Patidar *et al.,* 2018). The selection of suitable vector, signal peptide and expression systems are very crucial for successful chimeric proteins production. Although the advanced bacterial expression systems provide ease to the work, but selection of mammalian expression systems (e.g. CHO cells and COS cells) is preferable choice for therapeutic productions because the problem of endotoxin is related to the bacterial systems (Manoj *et al.,* 2017; Patidar *et al.,* 2018).

Advantages of chimeric proteins

The short half-lives of many immune mediators like cytokines and other effector proteins limit their bioavailability and therapeutic potentials (Manoj *et al.,* 2017). To achieve the maximum response, it needs multiple doses and higher concentration, but also increases the side effects, overall cost, and large scale production. Here the importance of CPs comes into the picture. By fusing these effector molecules to any suitable base like IgFc or carrier proteins such as albumin or transferrin, not only its half life can increased but also one can make it more specific and efficacious. For example, IL-2 is a classic cytokine, used in immuno-therapy. The shorter half-life of rIL-2 requires multiple doses and increase localization of rIL-2 induces side effects such as vascular leakage syndrome, hypoalbuminemia, edema, fever, anemia, hepatic and renal failure, thrombocytopenia, pulmonary and cardiac distress. To avoid these side effects researcher fused hIL-2 with IgG1Fc (Landolfi NF, 1991). The half life of rIL-2 in chimeric hIL-2/IgG1Fc is prolonged and this therapy shows high paracrine activity of rIL-2. This CP induces efficient antitumor T-cell response by enhancing the Ag-specific T-cell responses and by reversing the T-cell anergy (Landolfi NF, 1991).

Application of chimeric proteins

Human serum albumin bases chimeric proteins are being tested as anticancer drug where efficacy of drugs along with the stability is found to be increased (Ke Ren, 2013). Levemir is approved for the treatment of diabetes (http://www.levemir.com/). Albuferon is in phase III clinical trials for the treatment of hepatitis C (Chemmanur and Wu, 2006). Ozralizumab is in phase II clinical trial for treating rheumatoid arthritis (http://www.ablynx.com/rd-portfolio/clinical-programmes/ozoralizumab/).

Due to wide expression of transferrin receptor, transferrin is a choice of delivering the drugs, and proteins. Especially the presence of transferrin receptors in blood brain barriers increases the suitability of many therapeutic for brain related disorders (Kim *et al.,* 2010). The chance of proteolytic degradation of transferrin based chimera is very low, because transferrin are resistant to trypsin and chymotrypsin (Kim *et al.,* 2010). The chimeric proteins having

Granulocyte colony stimulating factor (G-CSF) and transferrin is able to transport through epithelial cells and maintain bioactivity thus it might be suitable for oral delivery (Bai & Shen, 2006). Similarly the chimeric protein of insulin with Tf is also able to transport through epithelial cells and maintain bioactivity. Human low-density lipoprotein receptor (LDL-R) and rabbit transferrin is being investigated to reduce the Plasma LDL Cholesterol (Ferrari, 2004).

Apart from albumin and transferrins, Fc portion of Immunoglobulins is a superior choice for the designing of chimeric proteins due to their specificity and longer half-life (Czajkowsky, Hu, Shao, & Pleass, 2012). The chimeric protein of tumor necrosis factor receptor super family member 4 (TNFRSF4) and IgG reduces the T cell-mediated colitis. The chimeric protein having hIL-2 and IgG1Fc has antitumor T cell response (Landolfi NF, 1991). Abatacept (Orencia, Extracellular domain of human CTLA-4 and IgG1 Fc) treats the Rheumatoid arthritis (Cagnotto *et al.,* 2020).

Conclusion and future perspective:

The therapeutic potential of chimeric proteins has attracted not only the researchers, also the pharmaceutical industries to use them as therapy, agriculture sectors and many other fields. Hence the designing and production of recombinant proteins has become the priority of R&D of many biotech industries as well as research institutes. Each big Pharma/Biotech industry has chimeric proteins in their pipeline, and making them suitable for entering into the market. There is a visible competition among the researchers for production of novel chimeric proteins and targeting the current issues of human health. It is necessary to understand the current status of these biologic and try to increase the percentage of these work actually translated into market. The strategies for the production of efficient chimeric proteins and suitable linkers required systematic approaches as well as systematic *in silico* studies for the same (Manoj *et al.,* 2017; Patidar *et al.,* 2018).

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ROBOTIC NURSING: THE UPCOMIMG ROLE IN HEALTH CARE DELIVERY

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Abstract:

Nursing must continually adapt to changes in the healthcare system as well as the larger economic and social environment as it is an essential component of patient care. The ageing of the population is one of the main reasons causing these changes. Meeting the needs of patients and the elderly in hospitals, nursing homes, and at home becomes a societal challenge when combined with the current shortage of nursing and caregiving professionals. Nursing robots are gradually becoming a part of everyday life. The minds of human nurses can be at ease. Their occupations are safe, although some assistance has been provided to undertake the majority of the tedious nursing work for them. Hospital nurses benefit from robot nurses. Smaller interactive robots are being used to combat loneliness and inactivity in the elderly population, while larger robotic machines can be used to carry out physically demanding tasks like moving patients. Innovative technologies like nurse robots are extremely beneficial because there is a growing elderly population and not enough healthcare professionals to care for it.

Keywords: Robotic Nursing, healthcare system, patient care, Innovative technologies

Introduction:

The foundation of the healthcare sector is nurses, and historically, the nursing profession has made up the greatest portion of the healthcare workforce. Two issues that have an impact on the healthcare systems and the nursing profession are steadily rising healthcare expenditures and an ageing population. The ageing of the population is a significant fact that has larger economic and social ramifications.

The use of various technological solutions has been suggested as a solution to the current scarcity of nursing and caring workers as well as the rising expense of healthcare. "Ambient Assisted Living" is one of the technologies that has developed to support the independent living and aging-in-place ideals. These "smart home" technologies' goal is to support independent living by using a combination of sensors that are properly installed in a home setup. Magnetic switches, temperature sensors, photosensors, water flow sensors, motion sensors, force sensors, smoke detectors, and biosensors for vital signs are a few examples of such sensors. The activities of daily life may be captured by ambient monitoring systems, which can subsequently be used to: identify short-term emergencies; identify long-term alterations in health status. Although these

technologies are relevant to patient and senior care, additional analysis is outside the purview of the current effort, which is focused on robotics-related technologies.

Magnetic switches, temperature sensors, photosensors, water flow sensors, motion sensors, force sensors, smoke detectors, and biosensors for vital signs are a few examples of such sensors. The activities of daily life may be captured by ambient monitoring systems, which can subsequently be used to: identify short-term emergencies; identify long-term alterations in health status. Although these technologies are relevant to patient and senior care, additional analysis is outside the purview of the current effort, which is focused on robotics-related technologies.

In nursing homes, assisted living centres, and hospitals, nursing robots could supplement human caregivers. They can carry out physical demanding activities, deal with elderly people's loneliness and idleness, or be given mundane jobs like taking patients' vital signs. Telerobots that can be operated remotely can perform interactive caregiving tasks and act as interfaces for remote communication between medical professionals and patients, the elderly, or both. People who are disabled or elderly may be able to live healthy, independent, and productive lives thanks to assistive robots. Assistive robots are divided into two categories: "Socially-assistive" and "Physically-assistive," depending on their primary function. The former aid end users through social connection, whilst the latter do so through direct physical contact.

Within the broader context of telerobotics and telemedicine, improved capabilities for the aforementioned robotics technologies exist. In reality, the broader field of healthcare robotics, which also includes medical robotic systems, includes nursing and assistive robots. The latter has been a focus of ongoing research, and a number of systems have already been put in place for use in clinical settings. Currently, robotic systems are used in radiation therapy and other therapeutic procedures as well as surgical specialties like general surgery, orthopaedics, and neurosurgery.

In reality, using nursing and assistive robots comes with a number of difficulties, including technological, clinical, financial, insurance, psychological, social, and ethical ones. Challenges in terms of technology include telecommunications, safety, indoor navigation, manipulation, and integrating robots with already-existing in-hospital equipment. The connection to the hospitals' enterprise resource planning (ERP) and electronic health records (EHR) software systems is one of the key integration examples. Logistics operations and vital sign measurements are the corresponding jobs for nursing robots, respectively. On the other hand, it is anticipated that user perceptions and attitudes toward nursing and assistive robots will have a significant impact on the development and application of these technologies. This is pertinent from the viewpoints of the patients, the elderly, the nursing staff, and the caregivers.

Nursing robots

Both healthcare institutions for the elderly and hospitals have a place for nursing robots. Robots may efficiently ease nurses' workloads, allowing them to focus on tasks related to their primary responsibilities. Already, the distribution of food trays, medications, and laboratory specimens across a hospital has been supported by robotic equipment. Additionally, logistics related to the storage of medical supplies and equipment may be automated by robots. Beyond these duties, a more advanced function for robots would involve teaming up with nurses to complement their job and boost productivity. Robotic nurses can also lessen the amount of harmful substances or illnesses that human nurses are exposed to on the job. After receiving specialised training, nurses may take on the responsibility of managing and directing the operations of a robotic fleet within a hospital, generating

Robotic nurses will do physically difficult tasks like carrying or transporting patients. The assistance of robots will be a huge comfort for nurses and caregivers, especially while caring for immobile or disabled patients. Innovative technologies like nurse robots are extremely beneficial because there is a growing older population and not enough healthcare professionals to care for it. To increase the effectiveness and calibre of care that nurses and their paraprofessional staff can give to the patients, a mobile robotic nursing assistant (RoNA) is widely wanted. By delegating some of the more physically taxing tasks, such an assistant could enhance a nurse's working conditions and lower the risk of self- or patient damage.

Nurses may experience a significant reduction in physical stress thanks to specially built robotic systems that assist with patient transfers, ambulation, and lifting. Back discomfort and occupational disorders are widespread among caretakers. It is possible to assign laborious tasks to specially designed robotic devices, like transferring and moving patients. This element also points to broader studies on wearable exoskeleton technology. Exoskeletons may improve a person's physical capabilities by allowing them to lift heavier weights and preventing musculoskeletal disorders. Exoskeletons actually offer a substitute for fully automated robotic solutions, effectively maintaining human skills in the workplace.

Additionally, nursing robots might offer telemedicine services. Doctors can efficiently communicate with patients remotely using interfaces provided by robotic nurses that are compatible with telepresence platforms. Regular virtual visits when the robot travels to hospital wards using the onboard screen to create the necessary visual contact with the evaluated patients are typical scenarios. Giving robots the ability to navigate on their own is a particularly appealing feature in this direction since it eliminates the need for operators to manually navigate robots until a certain patient is found. The robot may also take the patient's vital signs periodically as needed for a diagnosis and standard clinical procedures.

In theory, the second scenario also includes the patient's home environment, delivering specialist care to residents and healthcare facilities located in far-flung and secluded regions.
Overall, caregivers that are electromechanical have certain advantages than their human counterparts, such as the ability to work constantly throughout the day. Robots, which may be programmed, have the ability to customise care and change to meet different demands. Robots can be integrated with other hospital technologies, like cloud-based EHR systems, which is crucial because it makes it easier to access a patient's entire medical history and ensures continuity of care.

Definition of robotic nursing

Robotic nursing is the use of autonomous mobile robots that are primarily designed and programmed for nursery-related tasks in hospitals, care facilities, or even homes to support nurses in better preventing, providing rapid treatment for, and providing medical care to people, especially the elderly and physically challenged ones. Currently, robot nurses are employed to complete a number of repetitive tasks, including taking blood pressure and blood sugar readings.

Socially assistive robot

An assistive robot that helps end users through social contact is known as a socially-assistive robot. Robots are more effective than any computer programme or smartphone mHealth application due to a natural human tendency to attribute human characteristics and intentions to mobile physical entities. The following section discusses some potential applications for socially-assistive robots, including (i) companion robots, (ii) supporting adults with dementia, (iii) encouraging physical activity, and (iv) offering post-stroke rehabilitation.

In order to maintain and enhance health status, support mental and physical well-being, and lower the risk of depression in senior people, regular physical activity is crucial. Robots can facilitate workout sessions, evaluate user performance, and provide real-time feedback while encouraging senior users to engage in physical activity. In Görer et al., two potential implementation difficulties for these robots were noted. First, the automatic interpretation of the coach's motions must be accurately reconstructed, and second, a robot's physical embodiment is distinct from that of the coach's. Robotics are also used in post-stroke rehabilitation and exercise, which typically entails carefully planned repetitive, active, or passive exercises. A movement therapy robot could offer a diagnostic in either situation.

Physically assistive robot

The maintenance of mobility and the capacity to operate items are two important aspects of independent living that are closely related to both the quality of life of the elderly and of patients. The loss of mobility in elderly populations is caused by a wide range of medical disorders, including strokes, neurological diseases, bone fractures, and a drop in muscular strength. Robotic solutions have been suggested to provide the support needed to stand up, sit

down, and walk in order to tackle this issue. Users of robotic wheelchairs benefit from autonomy, increased mobility, and safety. Architectural obstacles, such as curb rising and lowering, may be overcome with the right mechanical framework for the robotic wheelchair.

People with motor impairments like restricted hand and arm movements, severe spinal injuries, or tremors can benefit from properly designed assistive robotic manipulation systems. According to surveys, people with disabilities in this group have the following specific needs for assistive devices to perform activities: eating and drinking (feeding assistive devices); personal care (washing, shaving, applying cosmetics); handling objects (books, devices); mobility and access (opening doors); and general reaching and moving tasks. The aforementioned challenges can be addressed by either fixed or wheelchair-mounted manipulation systems.

Famous nurse robots

Healthcare robotics has advanced far beyond its infancy. Robotic nurses have made such a significant impact on the healthcare sector that they are now well renowned for it.

Machine Dinsow

Robot Dinsow is a patient care tool used in Thai and Japanese hospitals. It uses video monitoring to keep an eye on elderly patients and facilitates video chats with their loved ones. Additionally, it phone-alerts caregivers of patient activities. Additionally, it offers exercise and medication reminders as well as exercises with the elderly. Last but not least, it offers karaoke and games for enjoyment.

Robot Paro

All throughout the world, hospitals and long-term care centres use this seal-like robot. It encourages communication between patients and medical staff. Additionally, it aids in patient relaxation by mimicking a baby harp seal's voice. It also adjusts to patient behaviour in part thanks to its five sensor kinds, which include light, audio, temperature, posture, and touch. Overall, this robot aids in lowering patient tension, enhancing their motivation and relaxation, and enhancing their interaction with other patients and caregivers.

Robot Pepper

This humanoid robot welcomes visitors and directs patients to the appropriate department at the front desks of two hospitals in Belgium. It can distinguish between gender, 20 different languages, and emotions including surprise, joy, sadness, and wrath. Additionally, it is capable of deciphering nonverbal indications including head nods, grins, frowns, and changes in speech tones. Additionally, Pepper uses two high-resolution cameras as well as a 3D camera to "see." Additionally, it has shape recognition software that uses images that have been captured. The robot can move at a maximum speed of 3 km/h thanks to twenty engines, three multidirectional wheels, and six laser sensors, two ultrasound transmitters, and three obstacle detectors in its legs, which enable it to determine the distance of objects within a 3-meter range.

Lifting Robot

They help nurses lift or move patients, especially in an elderly care facility. The obvious advantage is that nurses do not have to risk damaging their own back health by lifting patients.

Stan the Man

Nurses and other healthcare professionals are trained using them. The robot is built to react to different treatments used by the student nurse.

Actroid-F

Only real nurses can be imitated by this robotic nurse.

Functions of nursing robot

- Reversing cognitive decline (for example, reminding patients to drink, take a medicine or attend an appointment). Elderly adults usually need to take several drugs, and refusal can have negative consequences.
- Making it possible for patients and caregivers to communicate more effectively, lowering the need for as many in-person visits.
- By gathering information and keeping an eye on patients, certain situations (including heart failure and high blood sugar levels) may be prevented.
- Helping people with household chores - Many people give up independent living because they are unable to cook, clean, or use a washing machine or microwave due to arthritis.
- A robot that can transfer a real person from a bed or wheelchair to a standing position. This bear can transfer a patient from the floor or a standing position, lift them
- Robots can be used as a communication tool if an elderly person is unable to use a modern device (due to low vision or dementia, for example) or does not wish to learn how to do so. Instead, they can ask the robot to perform the necessary task. Imagine saying to a robot, "Robot, contact my daughter," and the robot connects the call using Face Time or Skype-like software.
- Robots can remind you to eat, exercise, go to appointments, and take your meds.
- Why Relevant to each individual since people sometimes forget to check the lists they write.
- Robot provides limitless tolerance Eg:- A person with dementia will frequently ask the same question repeatedly. When asked five, fifteen, or forty times, most people get impatient. A machine doesn't.
- Plans and processes for discharge will be assisted by robots. They will be incorporated into all hospital technologies and monitoring so that we can identify patient decompensation early and more precisely. Patients will consequently have better health results.

- Robotic nurses will be able to triage patients in clinics, ERs, and through Tele-health services to streamline care and offer standardised approaches to symptom management with significantly fewer resources.
- With the push of a button, robot nurses will assist us in prioritising our care and scheduling tasks for our nursing shift. For nurses, charting will become less of a hassle and time-consuming.

Advantages of using nursing care robots

1. Assist people who are confined to beds: Robotic nursing assistants have a system created primarily to provide the most basic services to patients who are unable to leave their beds. In order to care for the patient's requirements at home or in a hospital setting, a nurse robot will remain permanently in the patient's room. The robot helps with duties around the house, wakes people up for their prescription, and, if programmed to, can even give medication.

2. Faster training: Compared to human nurses, robotic nurses require less training time. Because they may operate continuously throughout the year without needing breaks for maintenance, repairs, or refuelling, they are also less expensive to maintain. Robotic nurses do more activities, such as the riskier nursing chores that

3. A decrease in labour expenses: By lowering the cost of human labour in healthcare facilities, robotic nurses enable providers to charge patients substantially less for their services. There is a 65% decrease in the cost of human labour in some hospitals, particularly in Japan where there are many robotic nurses in the nursing care department.

4. Maintain records and carry out medical interventions: In the nursing care sector, robots can also handle additional tasks like accurately transcribing and storing vital medical data. Additionally, they support the medical staff's diagnosis and treatment of patients while working under the direction of less experienced healthcare workers without the assistance of doctors or higher-skilled professionals.

5. Friendship: In hospitals or nursing homes, patients who receive little to no visitors value the company provided by the robotic nurses, who keep them amused and content. Robotic nurses also assist elderly people and patients with chronic illnesses in regaining their independence, lessening the need for human caretakers and nursing facilities.

6. Aids in preventing cognitive decline: The robotic nurses are helpful for patients with cognitive decline concerns as well since they allow them to complete tasks at the appropriate times. They are reminded by robots when to eat, take their medications, go to appointments, and more. Throughout the entire year, including nights, working hours, and holidays, the robots perform this task with consistency and high accuracy. Robots, unlike people, never get tired and can work indefinitely without stopping.

7. Data gathering: Robots are also particularly effective at continuously monitoring patients and gathering information for life-threatening conditions like diabetes and heart failure. For the quickest response, they quickly relay the information to the human nurses or doctors.

Limitations:

Privacy compromise: Nursing robots may breach privacy if they deploy surveillance technology to see, record, and transmit all of the patients' behaviours and data. Although this function frequently aids in patient protection, it may eventually result in privacy violations for patients.

Workplace Issues: The demand for human nurses is also lower than it was a few years ago due to the advent of robotic nurses in the healthcare sector.

Conclusion:

Healthcare is surely a fascinating, fast changing sector of the economy today. A lot of aspects of our lives are currently being impacted by robots, and their uses go beyond the traditional ones in manufacturing. The broader category of service robotics—the non-industrial uses of robots—includes nursing and assistive robotics. In that regard, the use of autonomous and/or teleoperated robots in healthcare can increase productivity without lowering standards of care while lowering costs.

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HUMAN MILK BANKING - THE ADVANCE COMPETENCIES GAINED IN NURSING PRACTICE

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Abstract:

When it comes to feeding a newborn, the main objective is to promote the use of the infant's mother's breast milk, but if that isn't possible, donated breast milk is the next best thing. Collecting, testing, and pasteurising breast milk for use in hospitals or by moms who are unable to breastfeed is known as human milk banking. The first human milk bank opened in Vienna, Austria, in 1909, and a second one opened in Boston, Massachusetts, soon after. There are now numerous milk banks operating all over the world to assist with infant feeding concerns. The Infant and Young Child Feeding (IYCF) Chapter is concerned about the widespread use of formula feeds in infants because human breast milk banks are not easily accessible. This article explains the significance and necessity of advance practice as one of the most important parts of nursing. Feeding donor human milk to premature babies has been studied for its safety, efficacy, and cost-effectiveness. It explains the current situation of milk banking in India and other countries of the world, as well as the various donor selection criteria, current pasteurization procedures, and quality control measures.

Keywords: Human milk banking, Advance competencies, Nursing practice, postnatal mother, low birth weight baby.

Introduction:

Breastfeeding is the best method of newborn feeding since human milk is the only milk that is specially tailored to the needs of the human infant (1). According to WHO and UNICEF, using human milk from other sources should be the first choice when a mother is unable to breastfeed (2). Human milk banks should be made accessible as necessary. All women should be encouraged to breastfeed their children. Breast milk should be expressed and kept in storage when a mother is unable to give her child a direct feed because of a medical problem. Pasteurized donor human milk (PDHM) is the best substitute if the mother's own milk is unavailable or insufficient. (3, 4). India has particular difficulties due to the country's high rate of low birth weight infants and the VLBW population's severe mortality and morbidity. 20% of all newborns in our nation are low birth weight, and they have higher mortality and morbidity rates. In these infants, breast milk can significantly reduce their risk of getting sick. As a result, in

order to assist thousands of low birth weight and preterm infants, the government, medical professionals, and civil society must collaborate to spread the word about human milk banking.

An organised service for the selection of donors and the collection, processing, storage, and distribution of human breast milk for sick newborns is referred to as a "human milk bank." or low birth weight or premature babies or babies with deficiencies of sucking or getting breast feeding or babies or infants or children who are given human milk of others than their own by donor's to feed the new born babies or infants by the mother to support the babies for medical reasons [8,9].

The necessity to develop standards for the formation and operation of human milk banks in our nation arose from this goal. These guidelines are not intended to present detailed scientific literature; rather, they are an attempt to use scientific approaches to support the formation and operation of human milk banking.

Human milk bank norms -

- There are two stages to the screening process for becoming a donor. First, the donor must complete a detailed health history questionnaire. Her primary care provider receives a second form to check the correctness of her health self-assessment. For the following reasons, a potential donor may be ruled out.
- She hasn't recently received a blood transfusion or other blood products.
- She has not had a tissue or organ transplant during the previous 12 months.
- She regularly consumes alcohol or other addictive substances that have a similar effect.
- She does not regularly take prescription drugs or over-the-counter meds.
- She does not take any legal pharmaceuticals, massive doses of vitamins, herbal preparations with pharmacological activity, or cigarette products.
- She has never had hepatitis, a systemic illness of any type, or a persistent infection.
- She had no sexual contact with someone who was at risk for HIV or hepatitis in the previous 12 months.
- She is not alcoholic or does not regularly has more than two drinks per day.
- She has a positive HIV, HTLV, Hepatitis B, C, or syphilis blood test result.
- The donor mother is usually a mother who has delivered her baby in the hospital.
- The milk is collected from mothers who are in the hospital during their stay or on her follow up visits or check up to the hospital.
- The collection can be made from maternity wards, NICU, PU, OPDs.
- The expressed milk should be collected with the consent of the mothers after counselling them and the benefit of donation of their milk.
- The excess milk is collected only after the mother has feed her baby first.

- The milk collection is done under 2 different categories- mother of-
- Full term baby.
- Pre term baby.
- They are separated and marked for easy disbursement to those mothers falling under that category.
- The milk is collected hygienically. With the help of the breast pumps which could be manually operated.
- The collection is made by the trained staff for smooth and easy collection.
- Place of collection and date is marked on the container.
- Then the milk is sent to the human milk bank with roper details and cooler bags.
- After reaching the data is entered in the log book.
- The collected milk is prepared to be pasteurized at 66^0C for 30 min.
- The collection container are sterilized in the hot air oven/warmer. For 10 min. at 25^0C is destroy any living organism.
- The pumps accessories are to be sterilized daily by disinfectant in CIDEX 2% allowing it to remain for 20 min in a container and wash it with distilled water. Before put to use. They are sent for gas sterilization twice every month.
- The water in the shaker bath needs to drained daily and wash with disinfectants once in every week.
- The samples of pasteurized milk collected with the number and date of each container from which it is poured in the test tube, has to be sent to the lab for microbiological testing of any growth of colonies, the test tube should be sent immediately to the lab with the details in the log book with container no and date.
- If there is growth the test report will be termed as negative or unfit it means that the milk of that container is not good for distribution. The colour and the colon arrangement will have to be observed carefully.
- Taking a smear for gram staining biochemical test like peptone water TSI motility and citrate test need to be conducted this will enable to know which organism is present in the milk sample.
- The milk container of positive report has to be thrown away or discarded in the drain.
- 2cc of pasteurized milk are sent the lab for test with sterile mouth covered container.
- The sterilization between 2 burners at a distance of about 4 to 6 inches on both sides of the test tube while pouring the milk in the test tube.
- After removing the container should be kept in the freezer at 12^0C to 15^0C immediately without losing much time for cooling them.

- The container will have to wait for 24hr waiting for the reports to come from the lab on growth.
- After no growth conformation it should be separated and kept in the safe area ready for dispensing.
- The containers with reports of growth will have to be re asturized and tested by going through the process again. if growth is still present then it discarded[10,11,12]

The lab technician needs to look for the following:

- *Staphylococcus negative.*
- *Staphylococcus positive.*
- *Pseudomonas.*
- *Klebsciella*
- *Streptococci*
- *E. coli*

Storage:

- Container should always fill ¾th allowing space for expansion.
- Freshly expressed breast milk at room temperature 24^{0}C for 2-3 hr.
- Expressed milk to be stored for more than 24hrs up to 48 hrs at 18^{0}C in the refrigerator.
- Milk to be stored for more than 72hrs up to 7 days 0^{0}C to -5^{0}C in the deep freezer.
- More than 1wk up to 3 months at -12^{0}C in the deep freezer.
- Up to 12 months at -18^{0}C to -20^{0}C in the deep freezer.[13]

Throwing:

- The milk after removing from the freezer should be brought to room temperature by holding the container in the warm water or leave for few minutes outside or in the warm water. With the lid closed. Before feeding shake the container to blend any fat that has separated.
- Do not throw the stored milk in a microwave or boil the frozen milk. the milk once thawed should not be refreeze but used completely the unused portioned has to be thrown off [12,14].

Dispensing the stored milk:

- Keep the list of recipient their name address and contact nos.
- Get the NOC from the mother's recipient for feed her baby the milk of other mothers.
- Keep the records of the daily amount received and disbursed dosages.
- Always distribute the milk in small quantities to avoid wastage and spillage.
- The dispensing of milk in terms of mother of pre term and full term will vary in terms of quantity too [15,3].

The important aspects of human milk identification:

- The milk containing colostrum are rich in fats and heavy with pale yellow in colour.
- Normal milk would be normal in fat content and light yellow in colour.
- The milk of preterm mother would be watery white thin in nature([15,4,3)].

Donor requirements for breast milk:

Eligibility foe doner

- A lactating woman in good health, who practises good health-related behaviour, and who does not regularly use prescription drugs or herbal supplements (aside from prenatal vitamins, human insulin, thyroid replacement hormones, nasal sprays, asthma inhalers, topical medications, eye drops, and birth control methods that contain only progestin or low doses of oestrogen);
- Has enough milk after successfully breastfeeding her child, who is doing great;
- Is willing to submit to blood testing for infection screening.

Who is unable to contribute?

Donor requirements for breast milk:

If a donor engages in the use of illicit substances, tobacco products, or nicotine replacement therapy, they are ineligible to donate.

- Has had a positive blood test for HIV, HTLV, Hepatitis B or C, or syphilis; is suffering from HBV, HIV, HCV, or venereal diseases; has had a sexual partner who is; has engaged in high-risk behaviour for contracting them in the past 12 months; or has undergone an organ or tissue transplant; or has received any blood transfusions or blood products in the past 12 months.
- Had a blood transfusion in addition to an organ or tissue transplant
- Has mastitis, a fungal infection of the nipple or areola, active herpes simplex, or is taking radioactive or other medications, or has chemical environmental exposure, or over-the-counter prescriptions, or mega doses of vitamins, which are known to be toxic to the neonate and excreted in breastmilk; or
- Has mastitis or a fungal infection of the nipple or areola, as well as active herpes simplex or varicella zoster infections in the breast or thoracic regions.

Conclusion:

Real milk offers a wide range of advantages that artificial formula will never be able to match. Milk banks must be set up all over the nation, especially in the neonatal departments of all hospitals, given the high percentage of preterm births in the nation and the degree of malnutrition that contributes to such newborns' postnatal growth. Additionally, it's crucial to

spread knowledge about donor breast milk and its safety before launching any donor milk banking programmes.

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DIET, INFLAMMATION AND ARTHRITIS: A TRIANGLE DRAMA IN THE BODY

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Introduction:

Inflammation

Inflammation is a process in which your body's white blood cells and they make protect you from infection like bacteria and viruses. But in some diseases, like arthritis, your body's defense system -- your immune system -- triggers inflammation when there are no invaders to fight off. In immune diseases, your immune system acts as if regular tissues are infected or causing damage.

Inflammation types

Inflammation can be either acute or chronic. Acute inflammation goes away within hours or days. Chronic inflammation can last months or years

Conditions linked to chronic inflammation includes: Cancer, Heart disease, Diabetes, Asthma, Alzheimer's disease

Inflammation and arthritis

Some types of arthritis are the result of inflammation, such as: Rheumatoid arthritis, Psoriatic arthritis

Symptoms of inflammation: swollen joint, joint pain

Inflammation may also cause flu-like symptoms including: Fever, Chills, Fatigue/loss of energy, Headaches, Loss of appetite

Causes and effects of inflammation

When inflammation occurs, chemicals in your body's white blood cells enter your blood or tissues to protect your body from outsiders. This increases the blood flow to the area of injury or infection. It cause redness and warmth. Some of the chemicals cause fluid to leak into your tissues, resulting in swelling. The protective process can trigger nerves and cause pain.

Higher numbers of white blood cells cause irritation, swelling of the joint lining, and loss of cartilage over time.

Diagnosis of inflammatory diseases

The doctor will ask about your medical history. Focusing on:

- They ask the pattern of painful joints and whether there is a signs of inflammation
- If your joints are stiff in the morning
- Any other symptoms

They will also check the report of X-rays and blood tests reports for biomarkers such as:

- C-reactive protein (CRP)

- (ESR)Erythrocyte sedimentation rate

Will inflammation affect internal organs?

Inflammation will affect our organs as part of an autoimmune disorder. The symptoms depend on which organs are affected. For example.

- Inflammation of your heart (myocarditis) will cause shortness of breath or fluid buildup.
- Inflammation can cause shortness breath in lungs.
- Inflammation in your kidneys cause high blood pressure or kidney failure.

Inflammation treatment

Inflammatory disease treatment include medications, rest, exercise, and surgery to correct joint damage. And treatment plan will depend on several things, type of disease, your age, the medications you're taking, your overall health, and how serious the symptoms are.

The goals of treatment are to: slow down the disease process

- Avoid the activities that aggravate pain
- take medication to ease pain and anti-inflammatory drugs
- take physiotherapy treatment
- use braces, splints to lower stress

Medications

Many drugs will lower pain, swelling and inflammation. They can prevent or slow inflammatory disease.. The medications include:

- Nonsteroidal anti-inflammatory drugs (NSAIDs, such as aspirin, ibuprofen, or naproxen)
- Corticosteroids (such as prednisone)
- Antimalarial medications (such as hydroxychloroquine)
- Other medicines known as disease-modifying antirheumatic drugs (DMARDs), including azathioprine, cyclophosphamide, leflunomide, methotrexate, and sulfasalazine
- BiologiZÀ drugs such as abatacept, adalimumab, certolizumab, etanercept, infliximab, golimumab, rituximab, and tocilizumab

Foods that cause inflammation

Many foods may worsen the symptoms of inflammation. Such foods include sugar, trans fats, refined carbohydrates, and red or processed meats.

Sugar: A diet high in sugar may affect chronic inflammation by increasing inflammatory markers in the blood,.In addition, excessive sugar consumption will increase inflammatory markers in children and lead to chronic inflammation,. This study compared a daily sugar reduction of 46% with an 11% reduction of pro inflammatory markers in 11 children. researchers suggest that a reduction in the amount of sugar-sweetened drinks or alcohol , beverages consumed during childhood may result in future health benefits.

Trans fats: Trans fat acid may increase inflammatory markers and the risk of chronic inflammation, this will lead to diseases such as diabetes and cardiovascular disease. Trans fats

will increase the the levels of low-density lipoproteins (LDL) while reducing high-density lipoproteins (HDL). in beef and dairy products contain small amounts of naturally occurring trans fats, most trans fats occur when manufacturers add hydrogen to vegetable oil. Trans fats may appear on labels as hydrogenated oil and also present in processed foods, baked goods, fried foods, and margarine.

Refined carbohydrates: Refined carbohydrates have a high-glycemic, this can increase a type of protein called advanced glycation end (AGE) products, and this will increase inflammation.

Refined carbohydrates include white flour products such as: white bread and rolls, some crackers, white rice, some cereals, Red and processed meat

What is inflammation?

Acute inflammation is a signal from the body to injury or infection, this increases blood flow to the affected area. And White blood cells helps to rebuild damaged tissue, and acute inflammation will stops when the wound heals.

Chronic inflammation is a long-term condition that will develop gradually over.

Causes of chronic inflammation can include:

- prolonged infection
- exposure to toxic chemicals
- autoimmune disorders
- autoinflammatory disorders
- repeated cases of acute inflammation
- oxidative stress in the body

How can inflammation affect health?

Inflammation can create DNA damage that will cause cancer. Chronic inflammation is also related with inflammatory bowel diseases, ulcerative colitis and Crohn's disease, which will increase the risk of colon cancer. Inflammation is commonly present in people with heart disease and stroke

Other inflammatory conditions include: diabetes, chronic kidney disease, non-alcoholic fatty liver disease, autoimmune conditions, such as lupus, neurodegenerative conditions, such as Alzheimer's disease, arthritis and joint conditions, allergies and asthma, chronic obstructive pulmonary disease (COPD)

Foods which may have anti-inflammatory effects include

Many fruits and vegetables, apples, and cruciferous vegetables, are high in antioxidants and polyphenols which may Anti-inflammatory foods and diets. Inflammation is a part of the body's healing process, and will also help fight illness. And then if a person has recurrent or persistent low-level inflammation, some foods related to diets may help a person reduce the symptoms.

Foods

- Foods high in sugar or processed foods will worsen inflammation, healthy eating regime based on fresh foods, such as vegetables and fruits have anti-inflammatory effects.
- **Fiber**: Increasing dietary fiber will help to lower certain inflammatory cytokines, according to the Arthritis Foundation.
  Learn more about healthy high-fiber foods here.
- **Oily fish**: oily fishes contain omega-3 fatty acids, which will help reduce the body's levels of inflammatory proteins.
- **Nuts**: nuts will help reduce the risk of cardiovascular disease and diabetes.
- **Turmeric**: curcumin in turmeric will help to improve inflammatory health conditions. Learn more about turmeric here.

What happens when you eat inflammatory foods?

It can eventually lead to chronic diseases including heart disease, diabetes, certain cancers, and some diseases of the bowelWhile these side effects are among the more manageable, Titgemeier admits that, if inflammation goes unregulated, it can lead to an increased risk of developing asthma, allergies, autoimmune diseases (like rheumatoid arthritis, lupus, and multiple sclerosis), depression, Crohn's disease, ulcerative colitis,

Inflammatory Biomarkers

Blood counts (e.g., white blood cell count, red blood cell count, hemoglobin count)

- C-reactive protein (CRP)
- Erythrocyte sedimentation rate (ESR)
- Procalcitonin.
- Calprotectin.

C-reactive protein

CRP concentrations are a reliable early indicator of active systemic inflammation because it will help differentiate inflammatory from non inflammatory conditions and reflect the severity of the inflammatory insult.

CRP is recommended over ESR to detect acute phase inflammation in patients with undiagnosed conditions because it is a more sensitive and specific than ESR. 1CRP is a narrow range of normal values, usually <3-10 mg/L in the blood, in patients with infections or inflammatory conditions, levels will rise several hundred-fold. And than in critically ill patients and those in the intensive care unit (ICU), PCT has greater accuracy and will be preferable to CRP, given that the specificity and sensitivity of CRP are lower and peak levels may not correspond to the severity of inflammation.

Some common inflammatory diseases

- Fatty liver disease may be caused by poor diet, which are inflammatory response
- Endometriosis

- Type 2 diabetes mellitus
- Type 1 diabetes mellitus
- Inflammatory bowel disease (IBD)
- Asthma
- Rheumatoid arthritis.

DII

The Dietary Inflammatory Index (DII®) is a literature-based dietary score that was developed to measure the potential impact of a diet on the inflammatory status of an individual; a high DII score reflects pro-inflammatory potential of the diet, whereas a low DII score reflects the anti-inflammatory potential of the diet.

Components of DII

The Dietary inflammatory index consists of 45 dietary components, in which 9 components, including energy, carbohydrates, cholesterol, total fats, saturated fats, trans FAs, protein, iron, and vitamin B-12,and has pro inflammatory properties,

The first version of the DII debuted in 2009 (29). That version was based on scoring 927 peer-reviewed articles published in the biomedical literature through 2007 linking any aspect of diet to ≥1 of 6 inflammatory biomarkers: IL-1β, IL-4, IL-6, IL-10, TNF-α, and C-reactive protein (CRP).

The DII® explained

The Dietary Inflammatory Index™ (DII®) was created with the knowledge accumulated over many decades of research showing that diet exerts a major influence over systemic, chronic inflammation. And making feel achy and lethargic, chronic inflammation is associated with a range of chronic diseases including cancer, diabetes, and cardiovascular disease.

DII estimates the inflammatory potential of one's diet through data provided by having individuals fill out a food frequency questionnaire. DII® score is then used to educate and inform individuals about the quality of their diet.

For example, on the DII®, all dairy products such as yogurt and milk are classified as "highly inflammatory" while chili peppers are "anti-inflammatory." Says Hébert, " .The confusion will arises from a disconnect between the taste of the foods and their physiological inflammatory or anti-inflammatory properties on the body

Reviews

1) Lu *et al.* (2014) concluded that the antioxidant and anti inflammatory activity of functional foods prevent ROS. In this paper we review recent studies that have examined the potential molecular singling of antioxidants and anti-inflammatory effects of individual dietary phytochemicals from popular drinks and foods (eg – curcumin, astaxanthin and lutein).

The in vivo effects of inflammation and anti-inflammation on proposed molecular mechanism of dietary compounds			
The Dietary compounds	**The Effective concentration or dose**	**Examples or models**	**stimulation / oxidative damage**
Curcumin	400ml	Streptozotocin-induced diabetic rats	Cutaneous wound healing
	50mg/kg	Cadmium-polluted Water on rats	Cadmium toxicity in systematic Oxidative stress
	200mg/kg	Arsenic-induced hepatic injuries in Kunming mice	Oxidative stress
	200mg/kg	Hepatorenal oxidative injury in rats	Cecal ligation and perforation induced sepsis
	300mg/kg	Theoacitomide induction in mice Quail from birds	Hepatic fibrosis
	200 or 400mg/kg	ICR mice injucted with LPS	Heat stress
	3mg/kg	Infrasound induced neuronal impairment in SD rats	Systematic inflammation
	10mg/kg	Rats after subarachnoid hemorrhage	Microglia mediated inflammation
EGCG	75mg/kg	Obese mice	Neuro inflammation
	6mg/kg	Diabetic rats	None inflammation
Astaxanthin	0.05%	Guinea pigs with hypercholestrolemic diet	None iflammation
Lutein	0.1g/100g		Oxidative stress and inflammation in both liver and eyes

2) Tharesa C *et al.* (1999).concluded that the dietary treatment of inflammatory arthritis. in scientific literature validates the usefulness of fasting in the control of inflammation.

Elimination diets are very successful. Fasting fallowed by a vegetarian diet can produce sustained positive response measured clinically and laboratory variables of inflammation. In Omega 3 and omega 6 fatty acids have anti-inflammatory effects.

Experimental studies on n-3 fatty acids in RA. Abbreviations used; EPA eicosapentaenoic acid, DHA. docosahexaenoic acid, PUFA. polyunsaturated fatty acids, gel - morning stiffness, NSAID. nonsteroidal antinflammatory drug, LT. leukotriene, IL- interleukin, TNF. tumor necrosis factor.

First author, year	Subjects, study period	Intervention	Results
Kremer, 1985 (35)	37 12 weeks	1.8gm EPA; diet high PUFA, low in saturated fat	less pain and joint swelling, but rebound at fats the end
Kremer, 1987(36)	40 32 weeks	2.7 gm EPA 1.8gm DHA	less fatigue andjoint swelling, decreased LTB4
Magaro, 1988(37)	12 30 days	1.6gm EPA 1.1gm DHA	less disease activity; less neutrophil chemiluminescence
Van del tempel 1990 (38)	16 24 weeks	2.04gm 20:5 n-3 1.32gm 22:6 n-3	less gel and joint swelling, decreased LTB4, increased LTBS
Tulleken, 1990 (39)	27 12 weeks	2.0gm EPA 1.3gm dha	less pain and fewer swollen joints
Kremer, 1990(40)	49 24 weeks	27 mg/kg EPA 18 mg/kg DHA, 54 mg.kg EPA 36 mg/kg DHA 6.8 gm oleic acid (olive oil)	more improvement with high dose fish oils; decreased LTB4 and ILl; olive oil also helped
Neilsen, 1992(40)	51 12 weeks	3.6gm n-3 PUFA	Less gel, less tenderness
Skoldstam, 1992(40)	43 6 months	fish oil 10 gm/day	Decresed NSAID consumption
Eapersen, 1992(43)	32 12 weeks	3.6gm n-3 PUFA	improved Ritchie's index; drop in ILl; TNF and complement activation products unchanged
Kjeldsen-kragh, 1992(40)	67 16 weeks	3.8 gm EPA 2.0 gm DHA with doses of naproxen	fish oils mitigated impact of naproxen withdrawal
Lau, 1993(40)	64 12 months	10 MaxEPA caps/day	Decresed NSAID use
Geusens, 1994(46)	90 12 months	2.6gm n-3 vs 6gm olive oil	Decresed medication use only in n-3group
Kremer, 1995947)	66 30 weeks	4.6gm EPA, 2.5 gm diclofenac withdrawal	diclofenac could be stopped without a flare

3) Rosenbeum *et al.* (2010).conclude that the antioxidant and anti-inflammatoy diet method and supplements of osteoarthritis and rheumatoid artharitis.in this topic review the efficacy studies of antioxidant and antiinflammatory dietary supplements used to manage osteoarthritis (OA) and rheumatoid arthritis (RA) and make conclusions about their place in therapy. Glucosamine, chondroitin, and methyl sulfonyl methane were excluded. In this three studies support cat's claw alone or in combination for OA, and also two studies support omega-3 fatty acids for the treatment of RA. We will not recommend use of vitamin E alone; vitamins A, C, and E in combination; ginger; turmeric; or Zyflamend

Content of Zyflamend per softgel capsules

Plant (Botanical name)	**Allegedactive compounds**	**Amount**
Rosemary {Rosmarinus officinalis) leaf 100 mg supercritical extract of rosemary and 50 mg extract (23% totalphenolic antioxidants rosemary [TPAl-34.5 mg)	Roaemarinic acid,camphor,borneol,cineol	150mg
Turmeric {Curcuma longa) rhizome 10 mg supercritical extract (45% turmerones-4.5 mg) and 100 mg ethanolic extract (7% curcuminoids-7 mg	Curcumin	110mg
Ginger {Zingiber officinale) rhizome 54 mg supercritical extract (30% pungent compounds-16.2mg, 8% zingiberene-4.3 mg) and 46 mg ethanolic extract (3% pungent compounds-1.4 mg)	Gingerol,shagaol,paradol	100mg
Holy basil leaf (Orimww sanctum) extract (2% ursollc acicl-2 mg	Ursolic acid, eugenol, rosmarinic acid, methyl chavikol	100mg
Green tea {Camellia sinensis) leaf extract (45% polyphenols-45	Epigallocatechin, epigallocatechin gállate, epicatechin gállate	100mg
Hu zhang , root and rhizome extract (8% resveratrol-6.4 mg	Resveratrol	80mg
Barberry {Berberis vulgaris) root extract (6% berberine-2.4 mg	Berberine	40mg
Chinese goldthread {Coptis trifolia) root extract (6% berberine-2.4 mg	Berberine	40mg
Oregano {Origanum vulgäre) leaf supercritical extract (4% TPA-1.6 mg	Carvacrol, linalool, rosmarinic acid, thymol	40mg
Baikal skullcap {Scutellaria baicalensis) root ethanolic extract the (17-26% baicalein complex, including baicalein and baicalin- 3.4-5.2 mg, and 0.4-0.9% wogonin-0.08-0.18 mg)	Baicalin, baicalein, wogonin	20mg

4) Galland *et al.* (2010) concluded that the diet and inflammation. In this topic reviews the single foods on inflammatory markers in defined populations. Most of the studies reveal a modest effect of dietary composition on some inflammatory markers in free-living adults, in different markers do not vary in unison. Significant dietary influences have been established for glycemic index (GI) and load (GL), fiber, fatty acid composition, magnesium, carotenoids, and flavonoids.in a traditional Mediterranean dietary pattern, which is typically have a high ratio of monounsaturated (MUFA) to saturated (SFA) fats and ω-3 to ω-6 polyunsaturated fatty acid (PUFAs) and provides an abundance of fruits, vegetables, legumes, and grains, has shown anti-inflammatory effects

Foods associated with a decrese in inflammatory markers in human interventional studies

Food	**Study duration**	**Effect**
Extra virgin olive oil	1 meal	Decreased TXB2 and LTB4 in comparison with corn oil, non-virgin olive oil neutrophil airway influx in asthmatics
Tomato juice	10 days	Reduced TNF-α production by whole blood
Tomato drink	26 days	No change in CRP 58 Walnuts 1 meal
Whole tomatoes	28 days	Decreased monocyte mRNA for TNF-α and IL-6 with no change in serum levels
Walnuts	1 meal	Reduced CRP and fibrinogen
Red wine	4 week	No effect on CRP, TNF-α
Garlic powder	3 months	Reduced CRP, fibronectin and serum amyloid A in obese subjects
Flax seed flour	2 weeks	40-50% reduction of CRP in subjects with CRP>3 mg/L
Tea ,black	12 weeks	Decreased CRP and platelet aggregation in healthy men
Tea.black	6 weeks	No effect on CRP in men
Tea, green	4 weeks	No significant effect on CRP in male smokers
Cherries, sweet	4 weeks	Shows Reduced CRP , no effect on IL-6 in healthy adults

Leo galland *et al.,* 2010

4) Hursat *et al.* (2010) concluded that the dietary fatty acids and inflammation. This topic review the clinical trials have generally shown that the benefit from dietary n-3 polyunsaturated fatty acids. n-3 PUFAs may act to alleviate symptoms do arthritis .these experiments showed that the n-3 PUFAs reduce the expression of cartilage degrading proteases, cyclooxegenese 2 and inflammatory cytokines.EPA is more effective than DHA data provides the consumption of n-3 fatty acids as a part of healthy diet and perhaps in treating arthritis.

Some clinical studies on the efficiency of dietary n-3 PUFAs (Hursat *et al.*, 2010)

Parameter	Reference
Morning stiffness	+ NE + ++ + ++ NE NE
Onset of fatigue	+ ++ +
Grip strength	+ NE ++ ++ NE NE + NE +
Walk time	NE NE NE
Tender joints	++ ++ + ++ ++ NE +
Swollen joints	+
NSAID reduction	+ NE +
Pain	+ NE +

5) Aluno *et al.* (2020) concluded that the diet in Rheumatoid arthritis verses systematic lupus Erythematosus; any difference in this reviews the Diet may be a possible facilitator of RMDs due to both the direct pro-inflammatory properties of some nutrients indirect action on insulin resistance, obesity and associated co-morbidities. This consistent body of research has been conducted in rheumatoid arthritis (RA), while studies in systemic lupus erythematosus (SLE) are scarce and conducted mainly on experimental models of the disease. In this article aims to outline similarities and differences between RA and SLE based on the existing literature.

Comparison of data available about different dietary patterns and the risk of developing rheumatoid arthritis and systemic lupus erythematosus in normal subjects

Dietary pattern or nutrient N RA SLE
AHEI -2010 total score 76.597 D risk no association
AHEI-2010 alcohol domain 76.597 D risk no association (moderate intake)
AHEI-2010 red meat domain (low intake) 76.597 D risk no association
AHEI-2010 nut and legume intake 76.597 no association D risk (higher intake)
AMed 204.055 no association no association
DASH 204.055 no association no association
EDIP 173.560 I risk no association

AHEI, alternative healthy eating index; aMed, alternate mediterranean diet; DASH, dietary approach to stop hypertension; EDIP, empirical dietary inflammatory pattern.

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GREEN NANOPARTICLES – FABRICATION AND ITS APPLICATIONS IN HEALTH CARE SYSTEMS

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Introduction:

Nanotechnology is the most promising technologies of 21st century. Nanotechnology is a diverse, conventional approach based upon molecular self-assembly, to develop new materials with dimensions on the nanoscale. Generally, nanotechnology deals with developing materials, devices, or other structures possessing at least one dimension sized from 1 to 100 nanometers. The prefix nano is derived from the Greek word nanos meaning "dwarf," need and today it is used as a prefix describing 10–9 (one billionth) of a measuring unit. The term nanotechnology was first coined by Tokyo Science University Professor "Norio Taniguchi", he defined Nanotechnology as, the process of separation, consolidation and deformation of materials by one atom or by one molecule. The concept of nanotechnology was given by Nobel laureate Richard P. Feynman in 1959; he demonstrated the concept of manipulation of matter at molecular and atomic level, i.e., nanoscale, which is considered as the beginning of advanced nanotechnology.

Nanotechnology is one of the emerging and rapidly growing fields which have shown tremendous revolutionary developments in different fields of science including physics, chemistry, biology, and engineering, and its meaning varies with each field. The term Nanotechnology is defined as synthesis of nanoscale materials (with size less than 100 nm) possessing new functions and properties (physical, chemical, electrical, optical, and magnetic) by understanding, controlling and restricting of matter at nanometer level. The rapidity of nanotechnology has raised the possibility of using therapeutic nanoparticles in the diagnosis and treatment of human disorders. Nanotechnology utilizes nanobased systems for various biomedical applications. Nanoscale particles and molecules are a potential alternative for treatment of disease because they have unique biologic effects.

Nanoparticles

Nanoparticles are used in biomedical applications as they offer many advantages to larger particles such as increased surface to volume ratio and increased magnetic properties. Nanoparticles are defined as 'solid colloidal particles ranging in size from 10 to 1000 nm. A nanoparticle shows diverse chemical natures and can be, metallic and comprised of metal oxides, silicates and polymers. Nanoparticles can be produced in different morphologies such as spheres,

cylinders, sheets or tubes. The use of nanomaterials in medicine dates back to ancient times. Ayurveda, a traditional system of medicine practiced in the Indian subcontinent since the 7th century uses metal ash (*Bhasma*) to treat various diseases. *Bhasma* are metallic/mineral preparations treated with herbal juices or decoctions and exposed to a certain amount of heat, as in the puta system of Ayurveda. *Bhasmas* are widely recommended in India for the treatment of many disease conditions (Pal *et al.*, 2014).

Types of nanoparticles

Nanoparticles are broadly classified into two categories i.e., organic and inorganic based on their composition (Moghtaderi and Abargouei, 2018). Organic nanoparticles are claimed to be less toxic than inorganic ones due to their easy digestion within gastrointestinal tract, hence they mainly used in food industry. Metallic nanoparticles are used in biosensors, drug delivery, and in treatment of cancer, and among these, silver and gold nanoparticles are of prime importance for medical use (Nikalje, 2015). NPs are classified on the basis of their morphology, dimensionality, composition, uniformity, and agglomeration. Nanomaterials can be compared with the size of cellular organelles such as nano-size proteins. They can target the desired sites leaving other cellular machinery uninterfered. With regard to their morphology, they are available in different forms such as nanoprisms, nanobelts, nanorods, nanoplates, nanospheres, nanocubes, and nanotetrapods (Buzea *et al*., 2007).

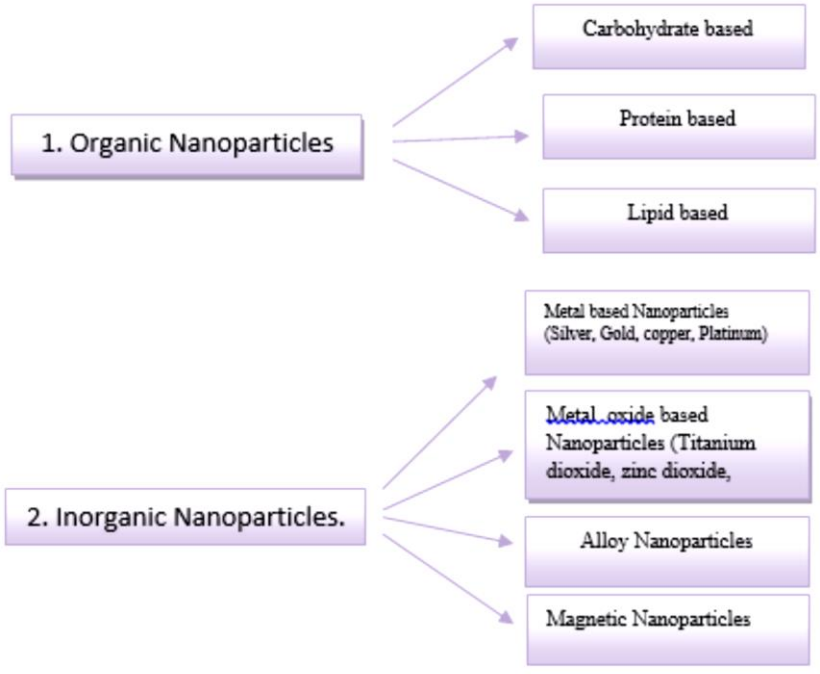

Figure 1: Types of Nanoparticles

1. **Metallic nanoparticle**

Metallic nanoparticles are small particles made of metal and can be synthesized by physical, chemical, or biological-based methods. Metallic nanoparticles were present with large

surface area, larger surface energy, specific electronic structure, Plasmon excitation and quantum confinement. Silver, gold, copper, palladium and platinum are the different types of metallic nanoparticles. Silver is the most preferred nanoparticle via green synthesis. Silver nanoparticles possess unique antibacterial efficiency, plasmon excitation and it contains wide range of applications in areas of medicine. Moreover, gold nanoparticles also contain considerable importance in many fields. The other nanoparticles have also been reported in low numbers.

2. **Metal oxide nanoparticles**

Metal oxide nanoparticles were synthesized by connecting the metal centers with oxo of hydroxo bridges, therefore producing metal - oxo or metal - hydroxo polymers.

3. **Alloy nanoparticles**

Alloy nanoparticles synthesized by combining different elements which can greatly extend the range of metallic nanoparticles and shows more stable structures with enhanced properties. Additionally, alloy nanoparticles demonstrate synergistic effects due to hybrid characteristics such as photocatalytic properties and super-magnetism. Therefore, alloy nanoparticles are being progressively studied for potentially diverse applications in the field of electronincs, engineering and catalysis.

4. **Magnetic nanoparticles**

Magnetic nanoparticles (MNPs) have widespread attention because of their unique features. Nanoparticles with magnetic properties are more advanced in that they can provide selective attachment to a functional molecule, confer magnetic properties to the target, and allow manipulation and transportation to a desired location through the control of a magnetic field produced by an electromagnet or permanent magnet (Ahn *et al*., 2004). These nanoparticles contain magnetic component (iron, nickel and cobalt) and chemical component with the specific functional ability. Due to the excessive range of attractive properties they have applications in catalysis, medical diagnostics and tissue specific targeting.

Synthesis of nanoparticles

Nanotechnology has applied in many fields including medicine and health care. Various methods can be used in the synthesis of nanoparticles. Such as chemical, electrochemistry, radiation, photochemical methods and biological techniques. During the production of nanoparticles, the particle size, chemical composition, crystallinity and shape of the nanoparticles can be controlled by temperature, pH-value, concentration, chemical composition and surface modifications. There are two basic strategies are used in the production of nanoparticles: “top-down” and “bottom-up” approach (Abobatta, 2018).

Top-down approach: A physico-mechanical method refers to the mechanical crushing of source material such as crushing, electroplating, laser-ablation, lithography, milling, and grinding are used for production of nanomaterials from bulk materials.

Bottom-up approach: There is production of uniformly distributed complex nanomaterials by self-assembly of small molecules. Different techniques like chemical vapor deposition, laser pyrolysis, liquid phase techniques, molecular self-assembly, and sol-gel processing are used for the synthesis of nanostructures using this approach.

Methods of nanoparticle synthesis

Nanoparticles can be synthesized from physical, chemical and biological routes. Generating nanoparticle through physical and chemical methods involves the use of toxic and harmful chemicals, which can emits toxicity to the environment. A biological method using various parts of plants and microbes considered as more beneficial and demandful technique for the bioproduction of nanoparticles called Green nanotechnology. Using less consumption of energy, moderate technology and no toxic chemicals, increases demand for this environment friendly technology. Nanoparticles synthesized using green technology may be more stable and efficient than the other mode of synthesized nanoparticles.

Green synthesis of nanoparticles

Bacterial mediated nanoparticle synthesis

Microorganisms employs largely in fabrication of nanoparticles due to its higher adaptation ability in metal concentrations and potential to reduce inorganic materials. Microbes convert these metallic ions into elemental form via an enzymatic reduction through their extracellular or intracellular routes. Bacteria are preferred over other microbes for the fabrication of NPs due to its feasible culture condition and ambient growth rate. Bacteria possess remarkable ability to reduce heavy metal ions and are one of the best candidates for nanoparticle synthesis. Various metal NPs, such as Ag, Au, Cu, Se and Fe and metal oxide NPs, such as silver oxide (Ag2O) copper oxide (CuO), zinc oxide (ZnO), titanium oxide (TiO2), manganese oxide (MnO2), magnesium oxide (MgO), iron oxide (Fe2O3), etc., have been fabricated using bacterial cells as a bionanofactory (Grasso *et al*., 2020).

Fungal mediated nanoparticle synthesis

Production of NPs using fungi is another biological method of NP synthesis. Higher chance of cell wall binding potential with metal ions and higher potential to tolerate metal concentrations, higher biomass and easy mode of culture, higher chance of metabolites bio-accumulation, fungi can yield a higher number of NPs than bacterial cells. Biofabrication of NPs using fungi is more efficient and inexpensive than bacteria, as fungi have a higher tendency to accumulate metals. The treatment of biomass and downstream processing of NPs is simpler in the fungi-based biosynthesis of NPs. Fungi have been widely studied for the synthesis of different NPs, such as silver, gold, etc. In the last recent years, the maximum work has been carried out on the extracellular fabrication of NPs using fungi, as it avoids the use of detergents; physical factors, such as ultrasound; and the doping of intracellular components, such as proteins, fats, nucleic acids, etc. (Gahlawat and Choudhury, 2019).

Figure 2: Methods of Nanoparticle synthesis

Yeasts mediated nanoparticle synthesis

Mycosynthesis of NPs is considered to be more straightforward and easy for stable production of NPs as compared to bacteria. Rapid growth and easy control of mass production, using simple nutrient culture medium altogether make yeast as the preferred microorganism for NP synthesis, as compared to other microbes. Yeast cells act as a template that induces biomineralization, which is the major mechanism for NP formation. Yeasts have the potential to survive in a high concentration of metal ions and have the capability to deposit a high amount of metal ions from a medium [14]. This feature of yeast has been used by different researchers for the green synthesis of NPs. Like bacteria, fungi and yeast have also been explored for the synthesis of various important metal oxide NPs. Aluminum oxide NPs (Al2O3NPs) are important metal oxide NPs which have significant antimicrobial properties against multidrug-resistant bacteria (Kumar *et al*., 2011).

Algal mediated nanoparticle synthesis

An autotrophic organism of algae can easily grow on minimal medium supplements. Algae cells have different secondary metabolites and many biologically active compounds which act as capping agents during NP synthesis and make the algal cell a unique “nanofactory” for the

synthesis of various NPs (Fawcett *et al*., 2017). Algae have been widely studied for the synthesis of different NPs, such as silver, gold, palladium etc.

Virus mediated nanoparticle synthesis

Viruses have been successfully used as a template for the synthesis of NPs. The capsid proteins of viruses (20–500 nm), provide an appropriate tenets to metallic ions to interact with virus machinery. It can be modified through genetic engineering for the synthesis of nanomaterials i.e. nanocomposites and nanoconjugates of metal NPs, for the treatment of cancer and targeted drug delivery (Gahlawat, G. and Choudhury, A.R. 2019). Plant viruses are much stable, easy to cultivate and nonpathogenic to animals and humans. Due to the ecofriendly nature, plant viruses can be deployed for the fabrication of NPs for use in humans and animals. Virus-mediated nanocarriers showed an increased penetration power in the tumor.

Plant mediated nanoparticle synthesis

Green synthesized nanoparticles shows predominant activity in pharmacological or therapeutic applications. Plant extracts can be used as the reducing agent/capping agent in the synthesis of nanoparticle. Nanoparticle synthesized from plant parts are cost effective, eco-friendly, may reduce their non-specific toxic behavior; hence it is highly safe for humans. They were different size and shapes of silver, gold, platinum and titanium nanoparticles and are synthesized from leaf, fruit, bark, pericarp and roots of plants.

The agents responsible for the reduction of metallic ions are the phytocompounds present in the plant extracts as polyphenols, terpenoids and polyols.(30). The nanoparticles produced from the plant source posses' remarkable antimicrobial, antioxidant, and catalytic properties derived from the phytocompounds which reduce into nanoparticle. They were found to be biocompatible for healthy cells and are lethal for pathogens, tumor and etc. Due to its simplicity and stability, nanoparticles were used in chemical sensing, biological imaging, antimicrobial, gene silencing and drug delivery (Wei and Qian, 2006).

Applicatons of green nanoparticles in healthcare system

Nanotechnology is gaining interest for research by many government and private organizations for research due to their applications in different sectors. Nanotechnology broadening the medical tools, knowledge and therapies. Nanoparticles are suitable and unique candidates which were applied in different fields due to its size, shape, structure and peculiar properties. They are in high demand commercially due to their wide range of applications in bioengineering, optical engineering, industries, electronics, cosmetics, textiles, defense and security, environment, energy, and more particularly in biomedical fields. Most commonly plant-derived green Ag and Au nanoparticles have been employed widely in health care systems due to less severe side effects in humans when compared to chemically synthesized NPs.

Nanomedicine, the application of nanotechnology in medicine draws on the natural scale of biological phenomena to produce precise solutions for disease prevention, diagnosis, and

treatment. Nanomedicine used in the treatment, screening, and diagnosis of a variety of diseases, including cancer. ZnONPs from a *Cassia auriculata* leaf extract, shown tumoricidal activity against MCF-7 breast cancer cells (Prasad et al., 2020). AuNPs produced from a *Trachyspermum ammi* seed extract inhibited cellular growth in HepG2 cancer cell lines (Perveen et al., 2021). NPs have shown encouraging results in the treatment of multidrug-resistant bacteria and might be a potential choice in the fight against such resistant pathogenesis. Ag has long been known for its antibacterial properties against a variety of bacterial strains. In particular, green AgNPs prepared from a *Carissa carandas* leaf extract demonstrated antibacterial efficacy against a variety of human pathogenic bacteria (Singh *et al*., 2021). Pathogenecity of NPs is more active against gram negative bacteria than the gram positive bacteria due to the difference in their cell wall structures. Due to the presence of single layer of peptidoglycan in the gram negative bacteria, SNPs can quickly damage them and prevent its proliferation (Ronovari *et al*., 2017).

Antioxidants used to treat aging and age-related diseases. The phytochemicals coated on the NPs surface have certainly a prominent influence in the observed antioxidant action. Some green plant-derived NPs have been described for their antioxidant potential as shown for AgNPs produced from a *C. carandas* leaf extract (Singh et al., 2021). Liposomes, TiO2, ZnO, dendrimers, nanoemulsions and nanocrystals were used in sunscreen, moisturizers and hair care products. The most of ionic and metallic nanoparticles have been reported in wastewater treatment and textile fabrics. AgNPs produced by *Matricaria chamomilla* showed effective catalytic activity against Rhodamine B under UV light, which could make it a promising material for wastewater treatment ((Duran *et al*., 2007). Nanoscience contributes to agricultural science and reduces environmental pollution through the production of pesticides and chemical fertilizers using nanoparticles and nanocapsules which have the ability to control or delay delivery. Nano based virus diagnosis, including the development of multiple diagnostic kit to detect the exact viral strain, biomarkers that specify the stage of diseases are the new advancement in the field of nanotechnology.

Conclusion:

The biosynthesized nanoparticles have worldwide applications in various disciplines. Green nanotechnology has emerged as standard tool for the production of environment friendly, non-toxic, cost effective green nanoparticles. Gradual development of nanotechnology-based methods has given a hope that soon life threatening and disabling disorders will be effectively treated.

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About Editors

Dr. R. Prabhu, M.Pharm., Ph.D., started his professional career posing his experience in Pharmaceutical Industry as a Production Officer in Mumbai during the year 1998 - 2001. After he has joined as professional service as Pharmacist in Health and Family Welfare, Government of Tamilnadu from 2001- 2005. Presently he is working as an Assistant Professor in the Department of Pharmaceutics, College of Pharmacy, Madurai Medical College, Government of Tamilnadu. He felt happy by contributing scientific research as an Author for research journals, review papers and Book chapters in reputed books. There are Two Patents on the name of Dr. R. Prabhu. He also received "Academic Excellence Award-2022" from Iterative International Publishers and obtained 'Excellence award' in teaching free GPAT classes conducted by Indian Pharmacy Graduate Association (IPGA) in 2021.

Dr. Med Ram Verma is presently working as a Principal Scientist at ICAR-Indian Veterinary Research Institute Izatnagar, Bareilly, Uttar Pradesh. He passed M.Sc. in Agriculture Statistics in 1998 from Dr. Y.S. Parmar University of Horticulture and Forestry, Nauni, Solan, Himachal Pradesh. He obtained his Ph.D. degree in Statistics in 2005 from Dr. B.R. Ambedkar University, Agra, Uttar Pradesh. He joined Agricultural Research Service in 2003. He guided 4 Ph.D. and 10 M.V.Sc students in the discipline of Biostatistics. He published 230 research papers in reputed journals. He authored/Edited 7 books. He was awarded with Best Teacher Award for the year 2014-15 by ICAR-IVRI Deemed University, Izatnagar, Bareilly, U.P. Dr. Med Ram Verma was awarded with prestigious Bharat Ratna Dr. C. Subramaniam Award for Outstanding Teachers 2018 by Indian Council of Agricultural Research on 16th July 2019. He is the Fellow of Indian Society of Agricultural Statistics and Elected Member of International Statistical Institute, Netherlands. He is the Editorial Board Member and reviewer of the several journals.

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Mr. Ajit Kumar Varma has obtained his B. Pharm from Gautam Buddh Technical University (GBTU), Lucknow, and M.Pharm from Rajiv Gandhi Proudyogiki Vishwavidyalaya (RGPV), Bhopal. He is currently working as an Assistant Professor at Faculty of Pharmaceutical Sciences, Rama University, Kanpur (U.P.), India. He has above Seven years of Pharmaceutical Industry and teaching in good experience. He has attened several National and International Conferences/Workshops Seminars. He has credit in Nobel Researchers Awards as well as Young Scientist Awards and published several research paper in International Journals, conferences and proceedings. He has been Reviewer of several Journals as well as different Membership of Educational Society.

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