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A BRIEF REVIEW OF WILD HIMALAYAN PEAR *PYRUS PASHIA*

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ABSTRACT: Within the Magnoliopsida class, *Pyrus pashia* is widely found throughout the Himalayan areas. *P. pashia* is a member of the Rosaceae family of medicinal plants. It's commonly called a wild pear. The plant has a range of nutritional and medicinal uses. In ethnomedicine, it is widely utilized as a hepatoprotective, inflammatory, antibacterial, antifungal, disinfectant, antioxidant, antimicrobial, and antidepressant to treat a wide range of illnesses. The genus *P. pashia* comprises approximately 38 species globally and contains approximately 160 phytochemical compounds, including primary and secondary metabolites such as alkaloids, glycosides, flavonoids, steroids, saponins, and tannins. Additionally, it contains useful polyphenolic therapeutic constituents like arbutin, flavan-3-ols, and chlorogenic acids. The phytochemistry, pharmacological activity, ethnomedicinal applications, and toxicological profile of *P. pashia* are all thoroughly updated in this review. This plant's scientific understanding as well as its potential for use in pharmaceutical research in the future, are critically examined.

INTRODUCTION:

Taxonomy and Origin: *P. pashia* is a medium-sized deciduous tree in the Rosaceae family that falls under the scientific category Maloideae [1]. *P. pashia* is primarily found in the Himalayas, which stretch from Pakistan to Vietnam and from the southern Chinese provinces to the northern regions of India [2, 3]. The common term for *P. pashia* is "wild pear." It is specifically utilized in the treatment of disorders pertaining to the digestive system [1]. The nutritional benefits of this plant's fruits are well known, and it is said that they are utilized to make herbal wines [4].

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India's woods are a valuable source of a wide variety of medicinal plants that have both therapeutic and preventive uses for human health. The wild fruit species may become valuable resources for pharmaceuticals and financial gains to meet the needs of good development and nourishment. One example of a wild fruit is *P. Pashia* (Kainth), a member of the Rosaceae family that is widely distributed in the Himalayan region with excellent ethnic advantages and is widely used by local communities to treat vascular, pulmonary, and gastrointestinal issues [5, 1, 6, 7].

The fruit of the Kainth plant is rich in several phytochemicals that have beneficial effects on fitness and is also high in vitamins. The authors from the Kainth fruit 2 have reported 28 significant phenolic compounds. Since, Kainth is extremely perishable when fully ripe and cannot be moved, it is classified as an underutilized fruit. Fruits should be priced to reduce waste, increase local

consumption, and enhance their value in the fight against malnutrition and other health issues [8]. Wood is a superior gas source in the crucial Himalayan region, and leaf extract is utilized as a tonic against hair loss. The leaves have a sour taste and are fed to lambs and goats [9]. The use of edible vegetation in the treatment of positive malignancies and cardiovascular illnesses is attributed to the presence of phenolic chemicals [10]. Taxonomically, *P. pashia* is one of the 38 species that belongs to the genus *Pyrus.* All species of this genus are found in tropical and subtropical regions of Asia, Europe and South Asia. Most species produce bioactive constituents, especially phenols and polyphenols are used widely in ethnomedicine [2].

Different Pyrus Species and their site of Origin [11]:

TABLE 1: SOME PRIMARY SPECIES OF *PYRUS*, GEOGRAPHICAL GROUP AND THEIR SITE OF ORIGIN

Geographic group	Species	Site of Origin
Asian pear species	*Pyrus armeniacifolia* T. T. Yu	China
	Pyrus baccata var. himalaica Maxim.	China, Bhutan, India, Nepal
	Pyrus betulifolia Bunge	China, Laos
	Pyrus calleryana Decne.	China, Korea, Taiwan, Vietnam
	Pyrus calleryana var. dimorphophylla (Makino) Koidz.	Japan
	Pyrus calleryana var. fauriei (C. K. Schneid.) Rehder	Korea
	Pyrus doumeri Bois	China, Taiwan, Laos, Vietnam
	Pyrus foliolosa Wall.	Burma, Bhutan, India, Nepal, China
	Pyrus harrowiana Balf. f.and W. W. Sm.	China, India, Nepal, Burma
	Pyrus lanata D. Don	Afghanistan, India, Nepal, Pakistan
	Pyrus sikkimensis Hook. f.	China, Bhutan, India
	Pyrus vestita Wall. ex G. Don	China, Bhutan, India, Nepal, Myanmar
Europe and Southern Africa.	*Pyrus aria* (L.) Ehrh. var. cretica Lindl.	North Africa, Middle East, Central Europe Oriental and Southern and Turkmenistan
	Pyrus boissieriana Buhse	Azerbaijan, Turkmenistan, Iran
	Pyrus caucasica Fed.	Eastern Europe and Central Greece
	P. communis var. cordata (Desv.) H.f.	UK, Portugal, Spain, France
	P. communis subsp. pyraster (L.) Ehrh.	Western Europe, Central Eastern, and Southern
	Pyrus domestica (L.) Sm.	Algeria, Cyprus, Eastern Europe Central West and Meridional
	Pyrus elaeagrifolia subsp. kotschyana	Turkey
	Pyrus praemorsa Guss	South of Italy, France
	Pyrus torminalis (L.) Ehrh.	North Africa, Middle East, South Caucasus, whole Europe
Americas	*Pyrus americana* DC	Greenland, USA, Canada
	Pyrus coronaria L.	Canada, USA
	Pyrus arbutifolia (L.) L. f.	USA
	P. coronaria var. ioensis Alph. Wood	USA
	*Pyrus diversifolia*Bong.	USA, Canada
	Pyrus fusca(Raf.) C. K. Schneid.	USA, Canada
	Pyrus floribunda Lindl.	USA, Canada
	Pyrus sanguinea Pursh	Canada, USA

Botanical Description: The leaves are petiolate, with a length of 4.5 to 11 cm and a width of 2.5 to 4.2 cm. The petiole is crenate, reticulate crenate, ovate to lanceolate, and has an acute apex to acuminate. The leaves are stipulate. One-year-old shoots have alternating patterns of leaf emergence. A single leaf with a stipule emerges laterally on each node of two years old branches. The axil is never without a thorn. The thorn also produces 2 to 30 pubescent, alternating leaves. On the fruiting spurs of older wood, there are five to seven leaves [12]. Fruit is a spherical berry. The size of the fruits varied from 1-2.5 cm in diameter. The surface of the fruit is dark greyish in colour bearing numerous densely distributed white and yellow spots. The fruit consists of fine wide radiating carpel chambers with one or two seeds attached in axile placentum [13].

Microscopic Characteristics [1]: *P. pashia* has undergone microscopic investigations to determine its morphological characteristics, which are useful in differentiating it from other species. The microscopic features of the plant are as follows:

Leaf: Simple, alternating leaves with a petiole are present. The lamina has an obovate or elliptical form, with a little hairy lower surface and a smooth top surface. There is spongy parenchyma and palisade in the mesophyll.

Stem: The bark is smooth and covers the cylindrical stem. The cortex is made up of thin-walled cells arranged in many layers. There is a coating of sclerenchyma fibres around the dispersed vascular bundles.

Root: *P. pashia* has a taproot root system, and its cortex is made up of parenchyma cells with a few strewn sclerenchyma fibres. Concentric circles comprise the arrangement of the xylem and phloem.

Flower: *P. pashia* flowers are hermaphrodite and have five petals, five sepals, and many stamens. The style is long and narrow, and the ovary is superior.

Phytochemical Screening: For a qualitative phytochemical examination to determine whether *P. pashia's* crude ethanol extract included any secondary metabolites, such as alkaloids, saponins, anthraquinones, coumarins, sterols, terpenes, flavonoids, and phenols [14]. Some of the major phytochemicals reported in *P. pashia* are listed below:

Flavonoids: Quercetin, kaempferol, luteolin, apigenin, and naringenin.

Phenolic Acids: Gallic acid, ellagic acid, chlorogenic acid, and caffeic acid.

Tannins: Condensed tannins, hydrolysable tannins, and proanthocyanidins.

Triterpenoids: Ursolic acid, oleanolic acid, betulinic acid, and maslinic acid.

Steroids: β-Sitosterol, stigmasterol and campesterol.

Chemical Constituents: In this plant secondary metabolites like Alkaloids, flavonoids, sterols, triterpenoids and phenolic compounds are present [15].

The methanolic extract of the fruits consists of d-Mannitol, 1,4-anhydro, Hexitol, Pentadecanoic Acid, 9,12-Octadecadienoic Acid (z, z), d-Mannitol, 1-o-(22-hydroxydocosyl), Octadecanoic acid, Squalene, Hexatriacontyl pentafluoro propionate, Stigmast-5-en-3-ol, (3. beta), Lup-20(29)-en-3-on, Lupeol, *etc.* [16].

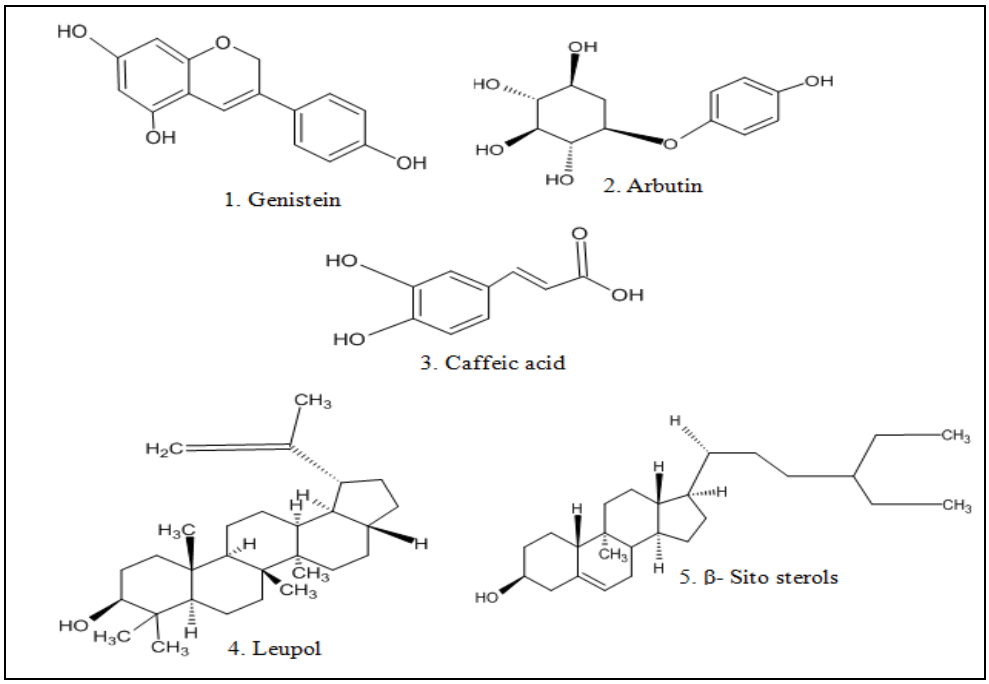

FIG. 1: CHEMICAL CONSTITUENTS OF PYRUS PLANT

TABLE 2: PHYTOCHEMICALS REPORTED FROM PYRUS PLANT

Sr. no.	Name	Part Used	Phytoconstituents	References
1.	*Pyrus pashia*	Stem	Hexacosanol, Hydroquinone, βsitosterol-β-D- glucoside, Luteolin glycoside. hen triacontanol, β-sitosterol, friedelin α-amyrin, Arborinol	17.
2	*Pyrus pashia*	Seedling leaves	Apigenin7-glucoside, Luteolin 7- glucoside, Luteolin 4 'glucoside, Chrysoenol 7-glucoside, Quercetin, Epicatechin, Catechin, Caffeoylcalleryanm, Caffeoyl arbutin, pCoumaroylarbutin, Arbutin, Acetyl arbutin	18.
3.	*Pyrus pashia*	Branches and Leaves	-3,5-Dicaffeoylquinicacid methyl 3,5-dicaffeoylquinate methyl 5-O-caffeoylquinate-4-Hydroxy-trans-cinnamomicacid 4-β-D-glucopyranosyloxybenzylester- 4-Hydroxy-cis-cinnamomic acid 4-β-D-glucopyranosyloxy benzyl ester p-Hydroxyphenyl6-O-trans-p-Coumaroyl-β-D-glucopyranosid e,p-Hydroxyphenyl 6-O-cis-p-Coumaroyl-β-D-glucopyranoside -4-Hydroxybenzoicacid - 4-(methoxymethyl) phenyl-1-O-β-D-glucopyranoside - 3,4-Dihydroxyacetophenone - 3,4-Dihytroxybenzaldehyde -Picein-Caffeic acid -trans-p-hydroxycinnamic acid - cedrusin- (+) -Isolarisiresinol - Arbutin, tannins, phloridzin, pectin, and amygdalin	19-21
4.	*Pyrus pashia*	Flowers	- 4-O-Z-coumaroylarbutin, 4-hydroxy benzaldehyde (35) -3,4-Dihydroxy benzaldehyde, 4-methoxy benzoic acid - 4-Methoxymethyl-phenol, 4-ethoxymethyl-phenol - E-1-(4'-hydroxyphenyl) -buten-1-en-3-one - 3,4-Dihydroxyl cinnamic acid; p-hydroxy acetophenone - Cynanoneside A, 4,4'-methylenediphenol - 3,3',4-Trihydroxy-diphenylmethane - Hydroquinone, arbutin, 6-O-acetylarbutin - 2-O-acetyl arbutin, 5-O-p-cis-coumaroyl quinic acid methyl ester- 5-O-p-trans-coumaroylquinic acid methyl ester - Gastrodin, 2-methoxy-4- (2- propenyl) phenyl β-D-glucopyranoside 3,5-O-caffeoylquinic acid, 3,5-O-caffeoylquinicacidmethylether - 8-C-p-hydroxy benzyl apigenin- 3, 5 ,7, 4'-Tetrahydroxy-8-methoxyflavone-3-O-β-D-glucopyranoside kaempferol 3-rutinoside, apigenin - Apigenin 4'-O-β-D-glucopyranoside; and apigenin 7-O-β-D-glucopyranoside	19.
5.	*Pyrus pashia*	Fruits	Sitosterol, lupeol, Chrysin	22.
6.	*Pyrus pashia*	Bark	Steroids and tannins	17.

Pharmacological Activities:

Antimicrobial Activity: Using the disc diffusion method, the antimicrobial properties of petroleum ether, chloroform, ethyl acetate, acetone, methanol, ethanol, and water extracts of the medicinal plant *Pyrus pashia* were evaluated against ten bacterial strains and three fungal strains (different gram positive and gram negative). The ethanolic bark extracts of *Pyrus pashia*, comprising distinct fractions of bark, fruit, and leaf, demonstrated noteworthy efficacy (17±1 mm, 15±1 mm, and 14±1 mm) against *Escherichia coli*, *Klebsiella pneumonia*, and *Shigella flexneri*. The extractive values of the fruit of the medicinal plant were evaluated in fresh part weight. The ash value of the fruit was 1.10 ± 0.05%), moisture content was 60.36±0.25%, crude fat content was 1.62±0.20%, and crude fiber content was 5.26±0.05%. According to the preliminary phytochemical analysis test, there were 28.38±0.12% of carbohydrates along with glycosides, alkaloids,

flavonoids, saponins, tannins, and unsaturated triterpenoids [23].

***In-vivo* Anti-inflammatory Activity:** Methanolic leaf extract from *P. pashia* has anti-inflammatory properties in albino rats. Five sets of six rats each were used in this investigation. Group 2 was given 100 mg/kg of the standard reference medication Indomethacin, Group 3 received 50, 100, and 150 mg/kg of the methanol extract with 2 ml of 1% vanillin, and Group 5 received 1% saline as the control group. To cause paw edema, the rats were intradermally injected with 0.1 ml of a 1% solution of carrageenan into the plantar surface of their right hind limb. Plethysmographic measurements of the paw volume were made both prior to induction (0 H) and four hours later at one-hour intervals. Groups II, III, and IV's paw volumes were contrasted with the controls. Therefore, both methanolic extract dosages demonstrated an inhibitory effect on paw edema generated by carrageenan, demonstrating an anti-inflammatory activity against acute inflammation [24].

Hepatoprotective: Aqueous extract of *P. pashia* in CCl4 -induced hepatotoxicity in mice: hepatotoxicity was produced by CCl4 30% in olive oil (1 ml/kg i.p.), and mice were given oral doses of 250 and 500 mg/kg b.w.t. of the extract for a period of 14 days. Pre-treatment (once daily for 14 days prior to CCl4 intoxication) and post-treatment (2, 6, 24 and 48 hours following CCl4 intoxication) groups were both present. The observed protective effect may be explained by several phytochemicals promoting the healing of liver injury. Additionally, the histological analysis validates the hepatoprotection [25].

Gastrointestinal, Respiratory, Cardiovascular: In vitro tests were conducted on isolated rabbit jejunum, tracheal, and aorta preparations using the crude ethanol extract of *P. pashia* fruits. The study included male and female rabbits of the local strain, weighing between 1.0 and 1.8 kg, that were acquired from the local market and had an age limit of 6 to 7 months. These were kept in the animal home in a climate-controlled setting (23–25°C). Standard food and tap water were given to the animals on an as-needed basis. The animals had free access to water but were denied food for twenty-four hours before the studies began.

For use in *in-vitro* research, rabbits that had suffered a hit to the back of the head were slaughtered. Via several pathways, the aqueous ethanolic extract of *P. pashia* demonstrated vasoconstrictive, bronchodilator, and spasmolytic properties. Although α-adrenergic, muscarinic, serotonergic, and angiotensin II agonistic components may be present, blockage of Ca2+ channels are most likely the mechanism behind the bronchodilator and spasmolytic actions. The phytochemical components of *P. pashia* fruits namely, alkaloids, flavonoids, glycosides, and anthraquinones are responsible for the Ca2+ channel blocking action [10].

Anti-depressant Activity: Methanolic *P. pashia* leaf extract has antidepressant effects on albino rats. Rats were split into four groups for this study: the first was the control group, which received only distilled water orally; the second group was the standard group, which received imipramine hydrochloride (15 mg/kg) as the standard; the third group was the test group, which received T1 (100 mg/kg); and the fourth group was the test group, which received T2 (200 mg/kg) (p.o.). In both test groups, methanolic extracts of P. pashia leaves (100 and 200 mg/kg) were utilized as T1 and T2, respectively. The results showed that there was an antidepressant effect in FST and LMA that was dose dependent. Caffeic acid and genistein, two compounds found in *P. pashia* leaves, may contribute to the plant's antidepressant properties [26].

Anti-Convulsant Activity: Ethanolic extract of *P. pashia* (EPP) fruit has anti-convulsant properties in albino rats. To explore a potential treatment mechanism for EPP, the anticonvulsant effect of isolated chrysin was tested against experimental animal models.

The maximum electroshock (MES) and pentylenetetrazol (PTZ) models of experimental epilepsy were used to assess the anticonvulsant activity in terms of the duration of the onset of hind limb tonic extension and convulsion of standardized EPP, respectively. In addition, chrysin's antioxidant effectiveness against PTZ-induced convulsion in experimental mice and its anticonvulsant and electrophysiological characteristics were studied. The chrysin's neurotoxic profile was also evaluated using the

rotarod apparatus and photo actometer for running and movement duration, respectively. In experimental rats, PTZ-induced convulsions and an acute form of MES were both significantly suppressed by EPP (100, 200, and 400 mg/kg). Additionally, rats given PTZ-induced convulsions showed notable anticonvulsant effect when given chrysin at doses of 2.5, 5, and 10 mg/kg. Furthermore, chrysin did not behave in a sedative-like manner in the rodent experiments. For the treatment of epilepsy, EPP may be a viable and different therapeutic strategy [27].

Medicinal Uses [10, 22, 24, 6, 27]:
Plant part: Fruit:

- It is a common diet item among tribal groups; it helps with constipation, reduces thirst, manages dysentery,
- It is beneficial for eye issues, sedatives, and leishmaniasis. Beneficial for treating dyspepsia and dysmenorrhea, Irritability, sore throat, and digestive issues, anaemia and abdominal pain.
- Dried fruit decoction enhances stomach and spleen function. Cattle fodder was added to increase the amount of milk produced.

Plant Part: Leaves and Branches:

- Provideas grazing for sheep and goats Leaf extract is used as a non-fermented beverage.
- It improves cosmetic appearance.
- In Chinese traditional medicine, it cures diarrhoea and abdominal pain
- It is a tonic for hair loss.

Plant Part: Flower: In the Chinese region of Yunnan, it is used as a health food to lower blood cholesterol and to treat diarrhoea, emesis, and cough.

Plant Part: Bark:

- Has both tonic and astringent qualities. Helpful in treating typhoid fever
- Used to treat fever, peptic ulcers, and gastric ulcers.

CONCLUSION: *P. pashia*, or wild Himalayan pear, is a common name for this plant (Kainth). It is well known that the fruits of this plant have nutritional value and are utilized to make herbal wines. The fruit of the Kainth tree is rich in several phytochemicals that have beneficial effects on fitness and is also high in vitamins. In the vital Himalayan region, wood is a first-rate gas supplier, and leaf extract is employed as a tonic against hair loss. *P.pashia* has undergone microscopic examinations to determine its morphological characteristics, which are useful in differentiating it from other species. Bioactive components, particularly phenols and polyphenols, are produced by most species and are extensively employed in ethnomedicine. This review examines pharmacological actions that include antibacterial activity, *in-vivo* anti-inflammatory activity, hepatoprotective activity, and activity related to the digestive, respiratory, cardiovascular, antidepressant, and anti-convulsant systems. This review includes a comprehensive update on *P. pashia* phytochemistry, pharmacological activity, ethnomedicinal uses, and toxicological profile.

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CONFLICTS OF INTEREST: The authors declare no conflicts of interest.

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BOMBAX CEIBA: A PLANT OF THERAPEUTIC POTENTIAL

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ABSTRACT: Medicinal plants have been utilized to treat a wide range of illnesses throughout human history. Plants are able to produce a wide variety of secondary metabolites, which are chemical substances that assist them defend against predators. The plants are significant for their therapeutic significance because of these organic ingredients, which also have various biological actions. Red silk cotton tree, or *Bombax ceiba* L., is a member of the Bombacaceae family of plants. *B. ceiba* is a tall tree whose components are used to treat a variety of ailments. These parts include the flower, leaf, gum, fruits, seed, stem bark, roots, heartwood and thorns. Essential phytoconstituents including lupeol, vanillin, anthocyanins, shamimin and mangiferin are found in *B. ceiba*. The herb has been used therapeutically in Ayurvedic, Siddha and Unani medicine, among other ancient medical systems. This page provides a thorough analysis of *B. ceiba's* pharmacological, phytochemical and therapeutic qualities.

INTRODUCTION: Plants are the source of many medicinal compounds that are utilized today to cure ailments like cancer, hormone imbalance, jaundice, diabetes, inflammation etc. [1]. Herbal medicine continues to be considered one of the most potent traditional natural medicines, even with the advancements in modern medical science [2]. The family Bombacaceae includes the medicinal herb *Bombax ceiba* (also known as *Bombax malabarica*), which is widely grown in China, India, Pakistan and Vietnam [3]. Plant appears in **Fig. 1, 2.** There are several names for it depending on the language, including the Indian kapok tree (English), the silk cotton tree, Shalmali (Sanskrit), semal (Hindi), shimul (Bengali), mullilavu (Malayalam) and kondabruga (Telugu) [4]. There are several applications for *B. ceiba* and its beneficial use has been documented in traditional Indian medical systems such as Ayurveda, Siddha and Unani [1].

The wood of *B. ceiba* is light-coloured, delicate and soft. It works well for light plywood and is in high demand as matchwood. Due to the cotton-covered seeds being carried a vast distance by the wind, it has spread widely [5].

Plant *B. ceiba* is used to treat wounds, leprosy, boils, asthma, diarrhoea and many other skin conditions. Its various parts are also used for their pharmacological activities, which include antiviral, antihypertensive, anti-inflammatory, antidiabetic, antioxidant and antibacterial properties.

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FIG. 1: A TREE OF *BOMBAX CEIBA*

FIG. 2: A TREE OF *B. CEIBA* IN FLOWERINGSEASON

There have been reports of several chemical components found in *B. ceiba*. The main chemical compounds found in plant parts (namely the flower, roots, bark and leaves) are Vicenin, quercetin-3-O-β-D-glucuronopyranoside, isohemigossylic acid, lactone-2-methyl ether, quercetin-3-O-β-D-glucuronopyranoside anthocyanin, shamimicin, 7-hydroxycadalene, quercetin, rutin, lupeol, quercetin-3-O-β-D-glucopyranoside, fraxetin, sexangularetin-3-O-sophoroside, vitexin, quercetin-3-O-β-D-glucuronopyranoside, isovitexin, kaempferol 3-O-β-D-glucuronopyranoside, benzyl-βD-glucopyranoside, kaempferol-3-O-rutinoside, scopolin, iso-mangiferin, hentriacontane, 7-O-methyl mangiferin, esculetin, phenylethyl rutinoside, protocatechuic acid, chlorogenic acid, scopoletin, methyl chlorogenate, blumenol C-glucopyranoside, vanillic acid and mangiferin. The structures of these compounds are shown in **Fig. 3** [6-11].

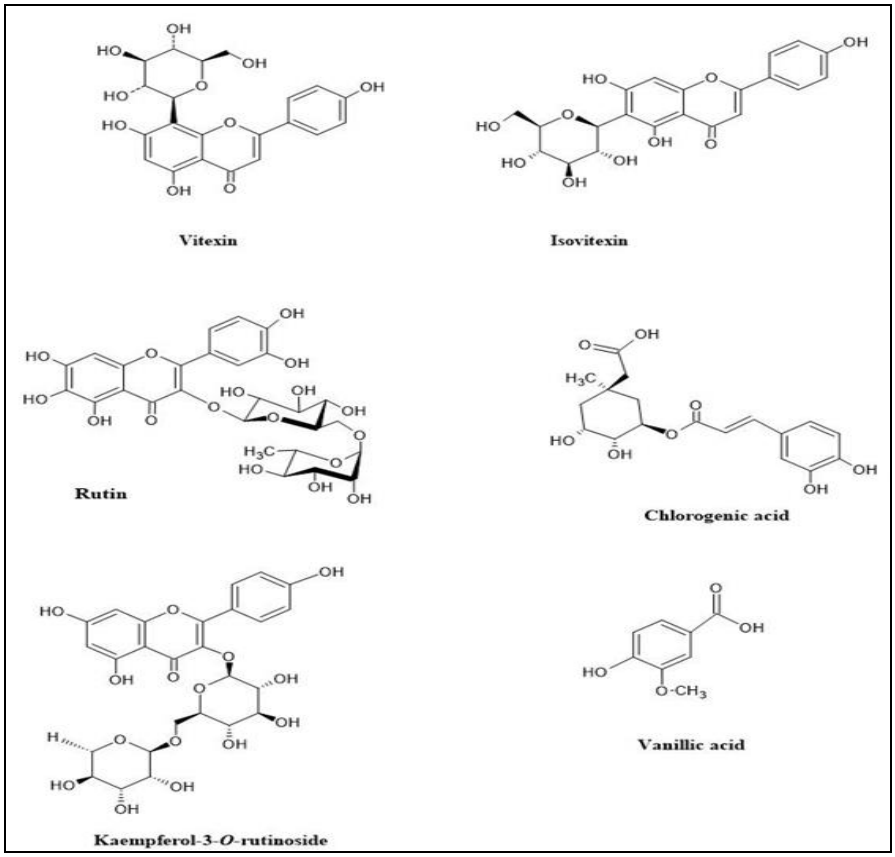

FIG. 3: PHYTO CONSTITUENTS OF *BOMBAX CEIBA*

Morphology: Plant *B. ceiba* grows from sea level to 1500 meters in height in India. Red silk cotton grows to a maximum height of 100 feet at a medium rate. Conical thorns are typically seen on the bark and branches of young trees [2].

Flowers-Many long, dense, silky-haired seeds are embedded in the massive, meaty, bright scarlet, yellow, or orange flowers [4]. As the leaves on the tree fall, the flowers bloom [12]. **Fig. 4** shows the plant's flower.

Leaves: The leaves are glabrous, big and spread apart. *B. ceiba* leaf is depicted in **Fig. 5** leaflets are lanceolate, 5-7, and 10–20 cm long [4, 13].

Bark: The tree's grey-brown or silver-grey bark is adorned with sharp, pointed thorns that resemble cones [12]. **Fig. 6** depicts the bark of *B. ceiba*.

Fruits: The tree produces brown, up to 55 mm-long fruits that contain many black seeds [12].

Seeds: Long, white wool with an irregular, oval shape encases smooth, black or grey seeds with dense, silky hair [12].

Gum: Semul-gum is a translucent, opaque and dark brown in color [12].

The tree grows along riversides and in deciduous forests, both wet and dry, all-over peninsular India. Deep sandy loamy soil or other well-drained soils are ideal for the tree's growth, especially in valley regions where the 50 to 460 cm of annual rainfall are uniformly distributed throughout the year. The tree grows swiftly and is a strong light-demander [14].

FIG. 4: *B. CEIBA* FLOWER

FIG. 5: *B. CEIBA* LEAVES

FIG. 6: *B. CEIBA*BARK

TABLE 1: TAXONOMICAL CLASSIFICATION OF *B. CEIBA* [11-13]

Rank	Scientific Name and common Names
Kingdom	Plantae – Plants
Subkingdom	Tracheobionta
Super division	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Dilleniidae
Order	Malvales
Family	Bombacaccac
Genus	*Bombax* L.
Species	*Bombax ceiba* L.
Binomial name	*Bombax ceiba* L.; *Bombax malabaricum* D.C.; Salmaliamalabarica (D.C.) Schott and Endl.

Phytochemical Analysis of Extracts of Various parts of *B. ceiba*:

Flowers: The flowers only contain fixed oils and fats, according to the petroleum extract; alkaloids, fixed oils, fats, phenolic compounds and flavonoids are contained in the acetone extract, while proteins, amino acids, glycosides, methanol and water extracts contain alkaloids, coumarins and flavonoids [15]. The blooms have been found to contain traces of essential oils, free β-sitosterol, quercetin, hentriacontanol, β-Dglucoside of β-sitosterol kaempferol and hentriacontane [11].

Leaves, Stem and Roots: The ethanol extract of fresh, undried *B. ceiba* leaves yielded a pale-yellow powder that was identified as shamimin, a

flavonoid C-glycoside that was recently discovered. Its 2-(2,4,5-trihydroxyphenyl)-3,5.7-trihydroxy-6-C structure was determined. One 12-glucopyranosyloxy-4H-1-benzopyran-4-one [12]. The leaves tannins, flavonoids, reducing sugars, steroids, saponins and anthraquinones were all found in the aqueous extract. Three bioactive compounds phlobatannin, alkaloids and saponins are present in the stem as opposed to two phlobatannin and alkaloids in the root [2, 16]. The presence of less bioactive compounds was demonstrated by the ethanolic extracts in comparison to an aqueous solvent. While the stem contained only flavonoids, the leaves also included alkaloids, saponins, and tannins. The root also contains just lowering sugars. Quantitative investigation shows that the leaves have high quantities of flavonoids (3.1%) and saponins (5.04%), but low levels of steroids (0.18%). The number of alkaloids (1.04%) and saponins (1.37%) in the roots was moderate. Merely 1.52 percent of the significant quantity of alkaloids discovered in the stem bark [2, 17].

Pharmacological Profile of *B. ceiba*:

Antiinflammatory Activity:

Bark: The human red blood cell (HRBC) membrane stabilization method was slightly adjusted in order to assess the bark extract's *in-vitro* antiinflammatory activity. Bark from *B. ceiba* shown a significant reaction and can reduce inflammation when extracted ethanolically. The findings indicated that, when compared to the standard, diclofenac potassium (50 mcg/ml) (74.07% inhibition rate), the ethanol extract at a concentration of 1000 mcg/ml demonstrated highly significant antiinflammatory activity ($p<0.001$) (62.96% inhibition rate) compared to the aqueous extract ($p<0.01$) (46.30% inhibition rate) and petroleum ether extract ($p<0.05$) (22.22% inhibition rate) [1, 18-19].

Flowers: Rats with paw edema caused by carrageenan were used to test the floral extract's anti-inflammatory properties. When compared to normal 2 mg/100 g.b.wt indomethacin (34.1%, 44.6%, 38.1%, 49.1%), the acute paw edema was reduced at 1, 2, 3, and 4 hours by 25 mg/100 g.b.wt (28.0%, 23.8%, 24.9%, 22.9%) and by 50 mg/100 g.b.wt (30.1%, 28.3%, 32.5%, 37.0%) of 70% methanolic extract [20].

Roots, Stems & Xylem: An aqueous extract (10 mg/kg body weight) of the plant's roots, stem and xylem significantly ($p<0.01$) decreased inflammation in carrageenan-induced paw oedema in Wistar rats by 79%, 74%, and 46%, respectively, compared to standard indomethacin [21].

Thorns: When compared to the industry standard diclofenac sodium, the hydroalcoholic thorn extract of *B. ceiba* demonstrated significant in-vitro antiinflammatory efficacy. At 500 µg/mL and 1000 µg/mL of extract concentration, the percentage of hypotonicity-induced stabilization/protection of human red blood cells (HRBC) membrane was determined to be 44.7% and 46.9%, respectively [22].

Antioxidant Activity:

Bark: The animals treated with *B. ceiba* methanol extract showed an increase in antibody titer values of 11.2 ±0.30 and 13.1 ± 0.27 and the delayed type of hypersensitivity (DTH) reaction induced by SRBC was also demonstrated to be substantial ($P<0.001$). The antioxidant activity was assessed at 150 mg/kg and 300 mg/kg (p.o.) doses. It also resulted in a significant decrease in lipid per oxidation (LPO) levels and improvements in the catalase (CAT), reduced glutathione (GSH), superoxide dismutase (SOD) activity and haematological profile [23].

The ethanolic and aqueous extracts antioxidant activity was assessed in a number of in-vitro models, including 1,1 di phenyl 2 picryl hydrazyl (DPPH) activity, 2,2 azino bis (3 ethyl benzo thiazoline 6 sulphonic acid (ABTS) activity, dimethyl sulfoxide (DMSO) activity, nitric oxide scavenging, superoxide dismutase activity, ferric ion reduction, total antioxidant activity, and lipid peroxidation activity at concentrations ranging from 50 µg/ml to 150 µg/ml. It was discovered that, up to the designated concentration, the extracts scavenged free radicals in a concentration-dependent manner in all of the models. When both extracts were compared to the standard (ascorbic acid), the results were almost the same [24].

The ethanolic bark extract shown good reducing power ability and outstanding in-vitro antioxidant activity against Nitric oxide and DPPH radicals; these results were statistically significant ($p<0.05$), suggesting that the extract is a useful source of

antioxidants. The ethanolic extract demonstrated 90% DPPH radical scavenging at a dose of 100 µg/ml, whereas the standard showed 92% DPPH radical inhibition. The extract's EC50 value was found to be 23.62± 1.99 µg/ml. The concentration at which the inhibition rate is 50% or the absorbance is 0.5 is known as the EC50 value [25].

Thorns: The capacity of the hydroalcoholic thorns extract to scavenge 1,1-diphenyl-2-picrylhydrazyl radical [DPPH] radical (41.62%) demonstrated its in-vitro antioxidant activity. Less than the absorbance of ascorbic acid (100µg/mL) ($p<0.001$), the absorbance of the thorn extract (100µg/mL) was 0.493 with 41.62% inhibition [22].

Flowers: Using methanolic flower extract, the antioxidant activity was examined. The EC_{50} for DPPH was 87 µg/ml, and the lipid peroxidation of soy bean liposomes and microsomes caused by peroxynitrite and ascorbyl radicals was 15 µg/ml and 105 µg/ml, respectively. The extract's K 0.5 value for inhibiting myeloperoxidase activity was 264 µg/ml. The ethanolic floral extract has little toxic effect on Vero cells [26].

Leaves: Crude extracts of *B. ceiba* leaves were reported to have in-vitro antioxidant activity (DPPH and ABTS + assay) in 95% ethanol leaf extract (0.012 ± 0.0003 mg/mL and 0.009 ± 0.0005 mg/mL, respectively) [27].

The chemical mangaferin, 2-β-D-glucopyranosyl-1,3,6,7-tetrahydroxy-9H-xanthen-9-one, had strong antioxidant activity in the DPPH assay. It was synthesized directly from methanolic extracts of *B. ceiba* leaves (EC50 = 5.8 (+/-) 0.96 µg/ml) [12].

Antibacterial and Antimicrobial Activity:

Stem Bark: Using the agar well diffusion method, the in-vitro antibacterial activity of a methanolic extract of *B. ceiba* stem bark was evaluated against three pathogenic bacterial strains: *Escherichia coli*, *Bacillus subtilis*, and *Klebsiella pneumonia*. The concentrations of the extract were 15 mg/ml, 30 mg/ml, 60 mg/ml, and 120 mg/ml. The extract was found to be effective against both Gram positive and Gram-negative bacteria even at lower doses ($p > 0.05$) [25].

Thorns: Under controlled conditions, the disc diffusion method was used to test the *B. ceiba* ethanolic plant extract's in-vitro antibacterial activity using the Muller Hinton Agar medium. The results showed that the ethanolic thorn extract had the largest zone of inhibition (ZOI) against *B. subtilis* (16.6 mm); nevertheless, at both 50 g/mL and 100 g/mL, the thorn extract showed moderate ZOIs against E. coli (13.6 mm) and *K. pneumonia* (11.3 mm) [22]. After assessing the thorn extract's antibacterial activity *in-vitro* against *Staphylococcus aureus*, it was determined that the silver nanoparticles exhibited noteworthy efficacy, exhibiting a 27.2 mm zone of inhibition at a minimum inhibitory concentration of 25 µg/Ml [28].

Antiangiogenic Activity:

Stem Bark: Methanol extract of *B. ceiba* stem bark has a strong antiangiogenic effect on human umbilical venous endothelial cells (HUVEC) in vitro tube formation. At dosages of 50 µg/ml and 30 µg/ml, luteol (found in the extract) strongly inhibits the formation of HUVEC tubes, with an inhibition rate of more than 80% at 50 µg/Ml [3. 18].

Antidiarrhoeal Activity:

Roots: The antidiarrheal properties of root methanol extract were assessed in Swiss-Albino mice at doses of 200 mg/kg and 400 mg/kg b. wt. throughout the first, second, third, and fourth hours of the test procedure [29].

Analgesic Activity:

Flowers: Using an electronically controlled hot plate, the analgesic activity was assessed on mice, the test subject. The test drug or 70% methanolic flower extract (50 mg and 25 mg of extract/100 g.b.wt.) administration caused the hind paw tendency to jump or lick before and after 1-2 hours of treatment. The mean reaction time was delayed, with percentage changes of 56.5% and 66.2% after 1 hour and 72.6% and 83.1% after 2 hours, respectively. The remaining group, on the other hand, showed a considerable delay with percentage changes of 48% and 68% after 1 and 2 hours, respectively, after receiving the medication tramadol (2 mg/100 g.b.wt.) 60 minutes before to testing [20].

Roots: The analgesic effect of treating Swiss-Albino mice with 200 mg/kg and 400 mg/kg b.wt. of the methanol extract of *B. ceiba* roots was assessed using the tail immersion method after 30,

60, and 90 minutes of treatment. The *B. ceiba* methanol extract showed significant peripheral analgesic activity, with percent inhibition values of 45.12% and 62.76% at 200 mg/kg and 400 mg/kg b.wt, respectively [29].

Hepatoprotective Activity:

Leaves: The extract from *B. ceiba* leaves exhibits liver-protective or hepatoprotective qualities. The phytosomes were made via the solvent evaporation technique. The ratios of 1:0.5, 1:1.0, 1:1.5, 2:0.5, 2:1.0 and 2:1.5 are provided by several formulations. With a maximum yield of 89.5%, particle size of 217.90±2.45, and entrapment efficiency of 71.25%, formulation F3 suggests that a 1:1.5 drug: lipid ratio is appropriate for complicated formulation. The absorption maxima of *B. ceiba* were determined to be 420 nm.

A typical graph showed linearity in the range of 10 µg/ml–60 µg/ml (R^2 = 0.9948). The compatibility of the *B. ceiba* methanolic leaves extract and excipients was evaluated using the FTIR peak matching method [18].

Roots: When an ethanolic extract of young B. ceiba (Et-BCYR) roots and metformin reduced serum levels of SGOT (Serum Glutamic Oxalate Transaminase) and SGPT (Serum Glutamic Pyruvate Transaminase) in Alloxan-Induced Diabetic Mice to 58% and 81.11%, respectively, the hepatoprotective activity was assessed. The values are the mean± standard error of three independent experiments. Et-BCYR's ability to lower SGOT and SGPT levels to 58% and 76.53%, respectively, indicates that liver damage may be treated with it [30].

Bark: The study assessed the hepatoprotective effect on diffused sinusoid enlargement, cell necrosis, and liver fatty degeneration. Specifically, the intravenous administration of an aqueous bark extract (1 gm/kg of body weight) significantly ($p<0.0001$) decreased aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in rodents (rats) induced hepatotoxicity [31].

Flowers: The hepatoprotective effect was studied in rats administered isoniazid and rifampicin to cause liver damage. The rats also received a methanolic flower extract at 150 mg/kg, 300 mg/kg, and 450 mg/kg i. p. which significantly decreased their levels of AST (aspartate aminotransferase), ALT (alanine aminotransferase), alkaline phosphatase (ALP), and total bilirubin. Additionally, there was a noticeable decrease in thiobarbituric acid reactive substances (TBARS) levels and an increase in glutathione (GSH) and total protein levels [32].

Hypoglycaemic Activity

Stem Bark: 50% ethanolic stem bark extract was shown to be hypoglycaemic at maximum tolerated doses of 50 mg/kg and 250 mg/kg in albino rats. This plant's ethanolic stem bark extract has hypoglycaemia properties [32].

Leaves and Flowers: Sprague-Dawley rats were used to test the ethanolic extract's hypoglycaemic potential. After six hours, a 500 mg/kg dose of the plant's leaves and flower extract significantly reduced the subject's fasting blood sugar level (26.6%) [33].

Roots: The ethanolic extract of *B. ceiba's* young roots was tested for hypoglycemia activity at 400 mg/kg. The extract may also have hepatoprotective, hypolipidemic, and hypoglycemic effects. At different times (0-24 hours), the blood glucose level was significantly ($p>0.05$) lower in (AIDM) Alloxan-Induced Diabetic Mice when an ethanolic extract of *B. ceiba* young roots (400 mg/kg bw) was given intraperitoneally. In 16 hours, there was 78.36% more activity than the average (72.36%) [19, 29, 30].

Bark: Using streptozotocin-induced diabetic rats, the ethanolic bark extract's hypoglycemic effectiveness was evaluated. The most effective dose for causing substantial ($p<0.001$) hypoglycemia and/or hypolipidemia effects is 600 mg/kg of *B. ceiba* ethanolic bark extract. Furthermore, as compared to rats with untreated AIDM at different time points (0-24 hours), this dose significantly ($p<0.001$) decreased the levels of total cholesterol and triglycerides in rats with severe diabetes ($p>0.05$). In 16 hours, there was 78.36% more activity than the average (72.36%) [34].

Cytotoxicity:

Flowers: The methanolic extract of *B. ceiba* flowers was used to study the cytotoxicity activities. contains four butyrolactones and two derivatives of ascorbic acid; it has been shown to

have protective effects against the cytotoxicity of benzo[a]pyrene (BaP) in HT1080 cells. Groups exposed to 50 µM benzo[a]pyrene showed cytotoxicity viabilities of 40% to 60% as compared to the groups treated with methanolic extract. Quercetin, Kaempferol, Butyrolactone derivative, and (-) Loliolide were among the identified compounds that lessened the cytotoxicity brought on by Mangiferin and 16 extract components [35].

Anti-obesity:

Stem Bark: The strong anti-obesity potential of the ethanolic extract at 200 mg/kg and 400 mg/kg against high fat diet-induced experimental obesity was evaluated due to the active flavonoids and lupeols present in the stem bark ethanolic extract of *Bombax ceiba* Linn. These compounds have the ability to modulate the Fatty Acid Synthase (FAS) and Protein Tyrosine Phosphatase-1B(PTP-1B) signalling in Wistar rats [36].

Anticancer Activity:

Leaves: Using the human leukemia cell line (HL-60), the 3-(4, 5-Dimethylthiazol – 2 - yl) - 2, 5-diphenyltetrazolium bromide (MTT) assay, caspase-3 activity, and cell cycle analysis were used to evaluate the extract's *in-vitro* anticancer efficacy. The antitumor efficacy of *B. ceiba* methanolic (BCM) leaf extract was assessed *in-vitro* using the HL-60 cell line.

After adjusting cell density to 1.5×106 cells/mL, cells were treated with BCM at concentrations of 1 µg/mL, 10 µg/mL, 25 µg/mL, 50 µg/mL, and 100 µg/mL for variable amounts of time. BCM at all concentrations decreased the viability of HL60 cells in a concentration-dependent manner. Between 1 µg/mL [(98.90± 0.43)%] and 10 µg/mL [(96.02± 1.08)%], While BCM caused significant cell death at 25 µg/mL [(75.14± 0.44%)] ($P>0.05$). 50 µg/mL [(68.91±0.21)%] and ($P<0.01$) (69.89 ± 0.09)%], 100 µg/mL ($P<0.001$) ($P<0.001$) [37].

Antipyretic Activity:

Leaves: The methanol extract of *Bombax ceiba* leaves (MEBC) was used to study the antipyretic efficacy in Wistar rats. When it comes to pyrexia caused by Baker's yeast, MEBC have strong antipyretic effects. The pyrexia caused by yeast is greatly reduced by MEBC (200 mg/kg and 400 mg/kg) ($p < 0.05$ and $p < 0.01$), respectively [19, 38].

Cardioprotective Activity:

Flowers: The heart's lactate dehydrogenase (LDL) was found to increase ($p<0.001$) in the aqueous flower extract of B. ceiba, while serum glutamic oxaloacetic transaminase (SGOT) and LDH were found to decrease at 150 mg/kg, 300 mg/kg, and 450 mg/kg b.wt. Additionally, the extract was found to have a protective effect against Adriamycin-induced myocardial infarction in rats [39].

Aphrodisiac Activity:

Roots: When the ethanolic roots extract (400 mg/kg body weight/day) was administered orally by gavage, the aphrodisiac effect was measured 12. Mount latency (ML), intromission latency (IL), ejaculation latency (EL), mounting frequency (MF), intromission frequency (IF), ejaculation frequency (EF) and postejaculatory interval (PEI) at 0, 7, 14, 21 and 28 days were the parameters that were observed prior to and during the sexual behaviour study. The ML, IL, EL, and PEI are all considerably reduced by the extract ($p<0.05$). The MF, IF, and EF were all considerably increased by the extract ($p<0.05$). These effects were seen in both sexually active and passive male mice [11, 18].

Hypotensive Activity:

Stem Bark: Evaluation of hypotensive activity was done at a dosage of 10 mg/kg. Rats with mean arterial blood pressure decreased by 58% after being exposed to a petroleum ether extract of *B. ceiba* stem bark (BCBP) [40].

Woods: The isolated chemical stigmast-4-en-3-one (1) of the petroleum ether extract of *B. ceiba* woods was used to evaluate the hypotensive action. It was found to be the active constituent, exhibiting a 55% reduction in blood pressure at a dose of 10 mg/kg [41].

Leaves: Shalimin, a C-flavonol glucoside included in the methanolic leaf extract of *B. ceiba*, was used to assess hypotensive activity. In Sprague Dawley rats, this dramatically lowered blood pressure at doses of 15 mg/kg, 3 mg/kg and 1 mg/kg [42].

Antianxiety Activity:

Leaves: Using the elevated plus maze method, the antianxiety effects of ethanolic extracts of *B. ceiba* leaves on rats were ascertained. The extract at 400 mg/kg significantly increased the amount of time

and entries into the open arm when compared to the control group (ethanol) and this difference was statistically significant (p value< 0.05). The most significant results were obtained with diazepam in comparison to the other groups (p<0.0005) [43].

Flowers: The hydroalcohalic extract of *B. ceiba* flowers (200 mg/kg and 400 mg/kg p.o.) was used to assess the antianxiety impact because it increases the number of mice that enter the open arm and their duration there in the elevated plus-maze paradigm [44].

Inhibitory Effects on Fatty Acid Syntheses:

Flowers: The minimal inhibitory concentration of *B. ceiba* ethanolic floral extract on fatty acid syntheses (FAS) is 247.98 µg/ml. Fatty acid syntheses (FAS) have been found to be hyperactive and overexpressed in the majority of malignancies [45, 46].

Stem Bark: When compared to the usual medication Gemfibrozil 50 mg/kg, the *B. ceiba* methanolic extract significantly (p < 0.05) reduced the increase in the levels of the serum indicators at 200 mg/kg and 400 mg/kg [36].

Diuretic Activity:

Fruits: Examining the diuretic effects of the aqueous and ethanol extracts from *B. ceiba* L. fruits, it was shown that at higher doses (200 mg/kg and 400 mg/kg, p.o., respectively), both extracts significantly increased urine production. Aqueous extract led to a considerable increase in urinary Na+ and K+ levels [47].

Antiosteoporotic Activity:

Stem Bark: The antiosteoporotic action of *B. ceiba* was investigated using its petroleum extract and methanol. At 100 mg/kg and 200 mg/kg, the two extracts considerably enhanced the osteoblast cell proliferation and alkaline phosphatase activity in UMR-106 cell lines. Additionally, it was found that administering petroleum ether and methanolic extract for 28 days significantly reduced the effects of ovariectomy-induced bone porosity and restored the bone's natural structure [48].

Nephrotoxicity Activity:

Leaves: Rats were exposed to gentamicin-induced renal damage, and the nephrotoxicity was assessed using *B. ceiba* ethyl acetate, n-butanol and aqueous leaf extracts. When co-administered with gentamicin (80 mg/kg) for 8 days, it was discovered that n-butanol and aqueous leaf extracts (200 mg/kg) protected the rats from changes in serum levels of urea, creatinine, and MDA (malondialdehyde) by reversing mild tubular necrosis rather than severe tubular necrosis [49].

CONCLUSION: The plant family Bombacaceae includes *B. ceiba* L. The tall tree *B. ceiba* is used to treat a wide range of illnesses. According to this review of the literature, traditional medicine has long employed a variety of *B. ceiba* Linn parts, including the flower, leaf, gum, fruits, seed, stem bark, roots, heartwood, and thorns, as a means of treatment. The chemical components that these plants create are diverse, as evidenced by the Bombacaceae family. The most significant isolated substances found in *Bombax ceiba* L. include phenols, anthocyanins, oxidized naphthalenes, sesquiterpenes, sesquiterpene lactones, triterpenes, steroids, lignans, alkaloids, amino acids, coumarins, long chain fatty acids and their esters, cyclopropenoid fatty acids, and carbohydrates. This review concludes that this herb has hepatoprotective, anticancer, cytotoxic, and abortifacient properties, among other uses. To make better use of this plant, however, more work needs to be done in terms of identifying and isolating the pharmacologically active compounds from various plant sections.

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A SYSTEMATIC REVIEW ON MUCOADHESION A NOVEL DRUG DELIVERY SYSTEM

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Keywords:

Mucoadhesion, First pass metabolism, Polymer, Systemic administration, Buccal drug delivery system

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ABSTRACT: The phenomenon known as mucoadhesion is characterized by interfacial molecular attractive forces between a natural or synthetic polymer and the surface of a biological membrane. This allows the polymer to stick to the membrane's surface for a prolonged period of time. The idea of mucoadhesion has garnered significant attention in many pharmaceutics sectors during the past forty years. The mucoadhesive buccal drug delivery system has numerous benefits that make it a unique drug delivery method for both local and systemic administration of different medications. The primary benefit of using this route for medication administration is that it avoids the initial metabolic stage of many methods circumvents the first pass metabolism of a number of medications that are susceptible to their first pass metabolism in the liver. Mucoadhesive drug delivery system contacts with mucus layer and generally increases the retention time of the dosage form at the specific site of absorption. The structural characteristics of the mucosa, the mechanism of mucoadhesion, various theories of mucoadhesion, are briefly discussed in this review to provide a brief overview of mucosal drug delivery.

INTRODUCTION:

Mucoadhesive Drug Delivery System: Mucoadhesive Drug Delivery Systems adhere to the mucosa layer and mucin molecules on the epithelial surface of the mucosa in order to increase the duration of time it takes for the medication to reach the absorption site. The drug that is designed for local effect or has the highest absorbency in the gastrointestinal tract requires a longer period of time to remain in the gastrointestinal tract.

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Mucoadhesive dosage forms are effective in enhancing both drug plasma concentration and therapeutic activity. The mucosal membrane is a greatlocation for administering drugs because it is easily accepted and applied. This is particularly valid for drug delivery systems that have mucoadhesive properties, as they release the drug by sticking to the mucous membran.

Initial metabolism in the liver, enzymatic degradation, difficulties with swallowing, and so on. Mucoadhesive delivery systems offer numerous advantages compared to conventional oral controlled release formulations.

Mucoadhesion / Bioadhesion: Early in the 1980s, controlled release medication delivery systems introduced the idea of mucoadhesion.

The process of two materials (at least one of which is biological) being held together for an extended length of time by intermolecular forces is called bioadhesion.

When an adhesive sticks to mucus or the mucous membrane, this process is known as muco-adsorption. Because these delivery systems can maintain a high drug concentration gradient throughout the epithelial system and extend the drug's residence time, they have been thoroughly studied in the pharmaceutical industry. The degree of bonding between the mucus surface and the drug-containing polymer is increased by muco-adhesion.

Advantages of the Mucoadhesive Drug Delivery System:

1. Drugs skip first-pass metabolism, which enhances bioavailability.
2. The drug is easily provided as therapy in an emergency situation.
3. Some medications that are not stable in the acidic environment of the stomach can be supplied by buccal administration.
4. Drug release throughout time.
5. In this system, drugs are absorbed through passive diffusion.
6. Adaptability in actual state, shape, size, and surface.

Mechanism of Mucoadhesion:

Contact Stage: This stage involves the interaction of the mucoadhesive polymer with the mucous membrane, where the formulation spreads and swells, allowing it to deeply engage with the mucus layer.

Consolidation Phase: This stage involves the activation and bonding of mucoadhesive material. The mucoadhesive substances become active when exposed to moisture. The presence of moisture softens the system which enables the mucoadhesive molecules to detach and join together through weak vander waals and hydrogen bonds.

Mucoadhesion Theories: An abundance of theories have been put forth to attempt to explain the mechanism underlying the complex process of muco-adhesion. These theories consist of:

Wetting Theory: The wetting theory is relevant to liquid systems that. Show a current attraction to the surface inorder to cover it. This connection can be identified through the use of measurement methods.

Like the contact angle. Overall, the rule dictates that if the contact angle is decreased, there will be a higher affinity. The contact angle should be zero or very close to zero to ensure sufficient ability to spread easily.

Diffusion Theory: According to diffusion theory, the strength of the adhesive force rises in proportion to the depth of penetration of the polymer chains. The rate of penetration is contingent upon factors such as the diffusion coefficient, flexibility, characteristics of the muco-adhesive chains, mobility, and duration of contact. The extent to which polymer and mucinchains can penetrate can be determined using the following equation

$$1 = (tDb)1/2$$

Where t is the contact time and Db is the diffusion coefficient of the muco-adhesive material in the mucus.

Mecanical Theory: According to mechanical theory, adhesion results from a mucoadhesive liquid filling in the imperfections on a rough surface. Furthermore, this kind of roughness expands the interfacial region that is accessible for interactions, therefore helping to dissipate energy and is arguably the process's most significant phenomenon.

Electronic Theory: In this theory, both mucoadhesive and biological components have opposite electrical charges and due to this when both materials come into contact electron transfer to form a double electronic layer which indicate the strength of mucoadhesive bond.

Adsorption Theory: According to the adsorption theory, the mucoadhesive device binds to the mucus layer by hydrogen bonds results in complete mucosal adherence.

Fracture Theory: This is the most widely recognized explanation based on mechanical measurements of mucosal adherence. It defines the link between the forces required to separate polymers from mucus and the strength of the adhesive bind. Work fracture is observed to be great when network strands are longer, or cross-links are weak.

Factors Affecting of Mucoadhesion: There are following types of factors are affect on muco-adhesion**:**

1. Polymer Related Factors:

A. Molecular weight

B. Concentration of active Polymer

C. Spatial confirmation

2. Environment Related Factors:

A. pH

B. Applied strength

C. Initial contact time

D. Selection of model substrate

3. Physiological Variables:

A. Mucin turnover

B. Disease status

Mucoadhesive Dosage Forms:

Tablet: Small, flat, and oval, tablets typically have a diameter of around 5–8 mm. Mucoadhesive tablets, unlike traditional tablets, allow for drinking and talking without causing significant discomfort, as they soften, adhere to the mucosa, and remain in place until they dissolve or release their contents. Generally, mucoadhesive tablets have the potential for use in controlled release drug delivery. However, combining mucoadhesive properties with tablets offers additional benefits, such as efficient absorption and improved bioavailability of drugs.

The high surface to volume ratio allows for closer contact with the mucus, making mucoadhesive tablets suitable for adherence to various mucosal tissues, including those in the stomach. This provides opportunities for both localized and systemic controlled release of drugs. Applying mucoadhesive tablets to the mucosal tissues of gastric epithelium is a common method for administering drugs for localized effects. Mucoadhesive tablets are popular due to their extended drug release, which reduces the frequency of drug administration and enhances patient compliance. However, a major limitation of mucoadhesive tablets is their lack of physical flexibility, which can result in poor patient compliance for long-term and repeated use.

Films: The high surface to volume ratio allows for closer contact with the mucus, making mucoadhesive tablets suitable for adherence to various mucosal tissues, including those in the stomach. This provides opportunities for both localized and systemic controlled release of drugs. Applying mucoadhesive tablets to the mucosal tissues of gastric epithelium is a common method for administering drugs for localized effects. Mucoadhesive tablets are popular due to their extended drug release, which reduces the frequency of drug administration and enhances patient compliance. However, a major limitation of mucoadhesive tablets is their lack of physical flexibility, which can result in poor patient compliance for long-term and repeated use.

Patch: Patches are laminates made up of an impermeable backing layer, a drug-containing reservoir layer that releases the medicine in a regulated manner, and a mucoadhesive surface for attachment. Patch systems are comparable to those used for transdermal medicine delivery. Solvent casting and direct milling are two processes for preparing adhesive patches. The intermediate sheet from which patches are punched is made using the solvent casting process, which involves casting a solution of the drug and polymer(s) onto a backing layer sheet and then letting the solvent evaporate. The direct milling process involves homogeneously mixing formulation elements and compressing them to the required thickness before cutting or punching out patches of a particular size and shape.

Gels and Ointments: Semisolid dose formulations, such as gels and ointments, offer the benefit of being easily dispersed throughout the oral mucosa. Semisolid dose forms may not provide accurate

drug dosing compared to pills, patches, or films. Poor gel retention at the place of application. has been overcome with the use of mucoadhesive compositions. Certain mucoadhesive polymers, such as sodium carboxymethylcellulose, carbopol, hyaluronic acid, and xanthan gum, undergo a phase transition from liquid to semisolid. This shift increases viscosity, resulting in the sustained and regulated release of medicines. Hydrogels are also a viable dose option for buccal medication administration. Polymers are hydrated in an aqueous environment and entrap drug molecules for delayed release through diffusion or erosion. Mucoadhesive gels offer long-lasting oral retention, effective medication penetration, and excellent patient acceptance. Adhesive gels are commonly used for delivering medicinal ingredients to treat periodontitis, an inflammatory condition.

Mucoadhesive Polymers: The Greek words "poly," which means numerous, and "meros," which denotes components or molecules, are the sources of the word polymer. Due to their special qualities, polymers compounds with large molecular weights made up of "monomers" are utilized in new drug delivery systems (NDDS). Polymers are the primary tool utilized in new drug delivery systems (such buccal drug administration systems) to control and prolong medication dose release.

Additionally, mucoadhesive polymers are employed in matrix devices, in which the medicine is placed within a polymer matrix that regulates the drug's release time. The core layer or the rate-controlling layer of the mucous membrane then allows the medicine to be released. One of the most crucial steps in creating a bucco-adhesive dosage form is choosing and analyzing the ideal bioadhesive polymer for the formulation. The oral drug administration is greatly enhanced by the use of bioadhesive polymers that cling to mucin and are effective.

Characteristics of an ideal muco-adhesive polymer:

- The polymer and its degradation products should be non-toxic.
- It should adhere quickly to moist tissue surface.
- The polymer must not decompose on storage or during the shelf life of dosage form.
- The polymer should be economic and easily available in the market.
- It should be inert and compatible with environment.
- It should form a strong non-covalent bond with the mucin-epithelial cell surfaces.

Advantages of Muco-adhesive Polymers:

- Provide prolong duration of action
- Reduce side effects
- Improve patient compliance
- Decrease dose frequency
- Localized delivery

Disadvantages of muco-adhesive polymers:

- Exhibit dose dumping effect
- Non-uniform distribution
- Cost effective

Mechanism of drug release from polymer:

Degradation: Biodegradable polymers undergo degradation as a natural biological process within the body. Following the release of the active components, the body removed them without altering bodily functions.

Diffusion: When a drug diffuses, it moves from the polymer matrix into the surrounding environment, which is the body.

Swelling: When dried polymers containing drugs are immersed in bodily fluids, the polymers swell and release the medication.

Classification of Mucoadhesive Polymers:

Based on Origin: Polymers of cellulose, polymers of acrylic acid, polymers of hydroxyethyl methylacrylate, polymers of ethylene oxide, polymers of vinyl pyrrolidone, and polymers of vinyl alcohol. Natural mucoadhesive polymers include chitosan, tragacanth, guar gum, Xanthan

gum, Sodium alginate, soluble starch, gelatin, pectin, and guar gum.

Based on Nature: This category's polymers are soluble in water. These polymer-developed matrices swell when placed in an watery media with the matrix dissolving later on. Greater mucoadhesive property is extended by the polyelectrolytes. For mucoadhesive qualities, other materials such as poly(vinyl alcohol), poly (vinyl pyrrolidone), hydroxypropyl methyl cellulose, and methyl cellulose have also been employed.

Polysacchrides and its Derivatives: Xanthan gum, gellan gum, guar gum, carrageenan, methyl cellulose, hydroxy propyl methylcellulose, hyaluronic acid, and several other polysaccharides and their derivatives have been used in ocular mucoadhesive delivery systems. It has been observed that cellulose and its derivatives possess surface active properties in addition to their ability to form films. In ocular administration systems, cellulose derivatives with lower surface acting properties are typically selected because they cause less irritation to the eyes. Sodium carboxymethyl cellulose has been discovered to have the best ocular mucoadhesive properties among the several cellulose derivatives. To create sustained delivery systems, cationic cellulose derivatives, such as cationic hydroxyethyl celluloses, have been combined with a variety of anionic polymers.

Hydrogels: Hydrogels are composed of polymer chains that are cross linked in three dimensions and possess the capacity to retain water due to their porous structure. The fundamental reason hydrogels can hold water is because they include hydrophilic functional groups, such as carboxyl, amino, and hydroxyl groups. Besides the drug targeting, mucoadhesive hydrogel-based formulations are used to increase the medication's bioavailability that is poorly soluble in water. This was explained by the delivery system's longer retention period in the digestive tract.

Impact of Physicochemical Properties on the Clinical Stability and Efficacy of Microemulsions: The stability of parenteral emulsions is crucial for their safe administration into the body. Instabilities in these emulsions, such as droplet aggregation and separation, are significantly influenced by their physicochemical properties. These properties include the composition and concentration of hydrophilic and hydrophobic components, surface tension, pH, degree of dissociation, droplet size, and the electrical charge on the droplet surface, along with their interactions.

The zeta potential, which reflects the surface electrical charge of the emulsifier, plays a key role in emulsion stability. A higher zeta potential increases electrostatic repulsion between droplets, thereby enhancing stability. Conversely, lower zeta potential can lead to instability. Additionally, high surface tension indicates a well-dispersed emulsion with stable oil droplets. Among these factors, droplet size is particularly critical; larger droplets pose risks such as embolism and reduced stability in the bloodstream, making them undesirable.

Research has demonstrated the relationship between physicochemical properties and the clinical performance of microemulsions. For example, stable emulsions of paclitaxel were successfully prepared using lecithin-sodium deoxycholate with polyethylene glycol further enhancing stability in plasma. Lecithin concentration was shown to improve emulsion stability, affecting both zeta potential and droplet size. The choice of emulsifiers and their impact on droplet size, influenced by pH, has also been explored, revealing important correlations between these properties and emulsion performance. Studies on phosphatidylcholine emulsions with purified egg yolk lecithin have highlighted the importance of droplet size in maintaining stability.

Future Directions: Microemulsions have diverse applications including targeted drug delivery, sustained and controlled drug release, enzyme immobilization, enhancing bioavailability, and taste masking. Since hydrophilic drugs can be unstable in the gastrointestinal tract, there is a need to explore biocompatible materials for targeted drug delivery. Additionally, water-in-oil (W/O) microemulsions can protect water-soluble drug molecules from metabolism. By converting W/O microemulsions into oil-in-water (O/W) microemulsions, it is possible to selectively release active pharmaceutical ingredients in targeted

regions of the gastrointestinal tract, enhancing therapeutic efficacy.

RESULT AND DISCUSSION: On this review we found that the recent global picture, scientists are finding various ways to develop buccal adhesive dosage form to improve the bioavailability of low oral bioavailability drugs. The research in this area continues to develop very quickly with more than hundred new papers being published each year. The current efforts in this area are focused on the design of mucoadhesive polymers with improved performance, development and validation of new physical techniques to study mucoadhesion and formulation of novel dosage forms for mucosal administration. Currently solid dosage forms, liquids and gels applied to oral cavity are commercially successful. The future direction of buccal adhesive drug delivery lies in vaccine formulations and delivery of small proteins/peptides.

Since, the introduction of Orabase in 1947, when gum tragacanth was mixed with dental adhesive powder to apply penicillin to the oral mucosa; the market share of bioadhesive drug delivery systems is increasing. The growth rate for transmucosal drug delivery systems is expected to increase 11% annually through 2007. Worldwide market revenues are at $3B with the U.S. at 55%, Europe at 30% and Japan at 10%.

Based on our current understandings of biochemical and physiological aspects of absorption and metabolism, many drugs, cannot be delivered effectively through the conventional are subjected to pre systemic clearance extensively in liver, which often leads to a lack of significant correlation between membrane permeability, absorption and bioavailability.

Exciting challenges remain to influence the bioavailability of drugs across the buccal mucosa. Many issues are yet to be resolved before the safe and effective delivery through buccal mucosa. Successfully developing these novel formulations requires assimilation of a great deal of emerging information about the chemical nature and physical structure of these new materials.

CONCLUSION: The main aim of buccal drug delivery of the drug as potential therapeutic agent is their instability in acidic environment, extensive first pass metabolism and low bioavailability of drug results an inadequate oral absorption. The buccal mucosa is rich in blood supply and relatively permeable. Mucoadhesive drug delivery systems or buccal drug delivery systems are gaining popularity day by day in the global pharma industry and a burning area of further research and development. This review presents the mucoadhesive or bioadhesive polymers, both conventional and substituted or conjugated emphasizing their mechanism of mucoadhesion. It can be concluded from the current study that research with conventional MDDS with conventional polymer is already a past trend. The reason is the maximum mucoadhesion occupancy with a single conventional polymer is already being achieved or studied. It is found from the current study that use of composite material, combined polymer systems, substituted or conjugated polymers are more popular to design a MDDS with desired criteria. Buccal drug delivery holds a great promise for systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules**.**

At the current global scenario, scientists are finding ways to develop buccal adhesive systems through various approaches to improve the bioavailability of orally less/inefficient drugs by manipulating the formulation strategies. Polymeric science needs to be explored to find newer mucoadhesive polymers with the added attributes of being biodegradable, biocompatible, non-toxic, mucoadhesive for specific cells or mucosa, and which could also function as enzyme inhibitors for the successful delivery of proteins and peptides. However, the invention of new biomaterials, tailor-made copolymers, has excellent potential for mucoadhesive drug delivery, but the formulations based on them still have to go a long way to find their path in actual clinical practice. Recently researchers facing many more challenges in development of such formulation and it requires a multidisciplinary approach.

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A COMPREHENSIVE INSIGHT INTO *ANETHUM GRAVEOLENS* COMPOSITION AND ITS MEDICINAL POTENCY

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Keywords:

Anethum graveolens, Composition and Medicinal significance

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ABSTRACT: *Anethum graveolens* (Dill) leaves and seeds of the plant are mainly used for traditional health treatments like diuretics and stomach disorders. Various observations of *Anethum graveolens* plant oil and other extracts showed antidepressant, analgesic, antiproliferative, antimicrobial, anti-inflammatory, analgesic, antioxidant activity, effects on gastrointestinal system, hyperlipidaemic effects, contraindications and adverse effects, and effects on reproductive system. Further, it is also used to prevent food spoilage or contamination. In the food industry, it is also used for flavoring foods. The important isolated molecules reported are carvone, dihydrocarvone, limonene, cymen, carvacrol, phellandrene, coumarins, flavonoids, phenolic acids, steroids, *etc*. The various traditional uses of the plant parts are stomachic and diuretic in Ayurvedic practices.

INTRODUCTION: The Apiaceae family is popularly known for its medicinal applications. The *Anethum graveolens* belong to this family and are uniquely known as dill, Sthatpushpi, Sowa, Soya, and Shibth (English, Sanskrit, Hindi, Punjabi, and Arabic). All parts of the plant are traditionally used for different medicinal applications such as antidepressant, analgesic, antiproliferative, anti-microbial, anti-inflammatory, analgesic, anti-oxidant activity, effects on gastrointestinal system, hyperlipidaemic effects, contraindications and adverse effects, and effects on reproductive system. Further, it is also used to prevent food spoilage or contamination. In the food industry, it is also used for flavoring foods. In Ayurvedic medicine also, *Anethum graveolens* seeds are used for diuretic and stomach-related issues.

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The important isolated molecules reported are carvone, dihydrocarvone, limonene, cymen, carvacrol phellandrene, flavonoids, phenolic acids, coumarins, and steroids. Many other molecules were extracted from seeds, like coumarins, steroids, and flavonoids [1-2] **Fig. 1.**

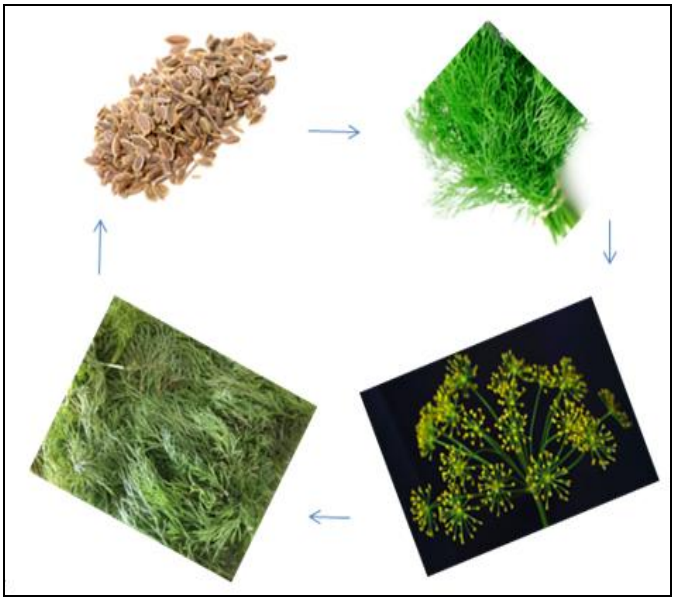

FIG. 1: *ANETHUM GRAVEOLENS* PLANT SEED, LEAF AND FLUORESCENCE

Chemical Constituents: The various chemical constituents that exist in different parts of *Anethum graveolens* were listed below [3-7] **Fig. 2.**

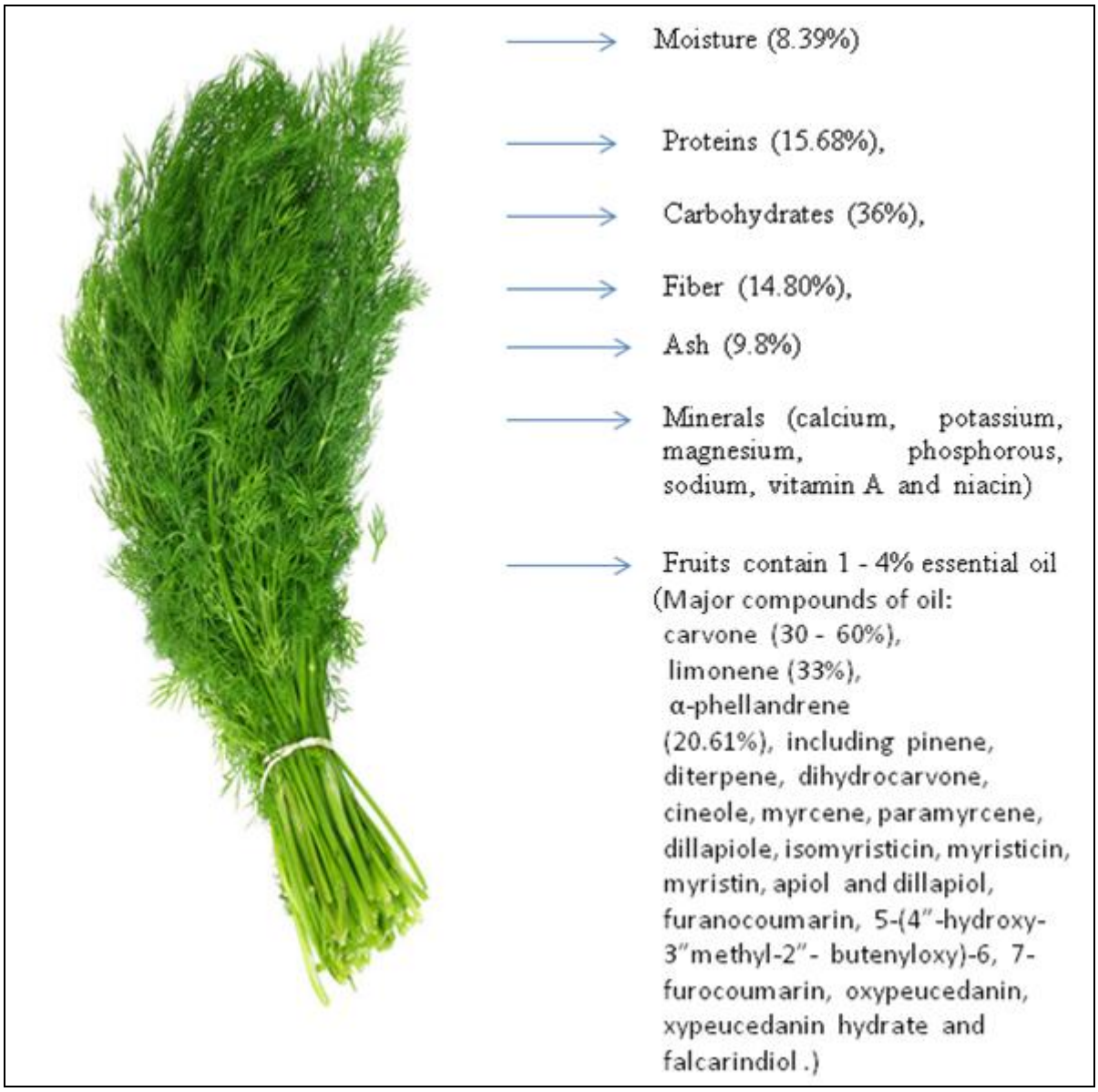

FIG. 2: CHEMICAL CONSTITUENTS OF *ANETHUM GRAVEOLENS*

Medicinal uses: Traditionally the aerial parts of the plant (*Anethum graveolens*) were practiced for different medicinal applications such as for colic pain, flatulence, diuretic, galactogogue, stimulant, stomachic, intestinal spasms, appetite, bad breath, stimulating milk flow, piles, urinary-related issues, and mental-related issues, and also used as condiments, tea, pickles, salads, sauces, and soups, flavoring in the food industry, perfume industry, detergents, and soaps [8–23].

Phytoconstituents: The phytoconstituent analysis of *Anethum graveolens* plant observed that terpenoids, glycosides, flvonoid, and tannins are the major constituents of roots, stems, and leaves [24].

Medicinal Significance:

Antidepressant Effect: The aqueous extract was given orally and showed excellent antidepressant potency in comparison with sertraline and tramadol, dose: 250 mg/kg body weight [25].

Antiproliferative Effect: Mohammed *et al.* (2018 reported that the *Anethum graveolens* seeds against the HepG2 cell line showed good antiproliferative effects by using the ethyl acetate fraction.

Further, it was observed that stems above parts of the plant are highly effective against uterus cancer [26].

Antimicrobial Effects: Chahal *et al.* 2017 observed that the existence of carvone and limonene in various extracts may be responsible for the various activities such as antimicrobial, anti-inflammatory, and antioxidant [27].

Hanan Y. Aati. 2022 reported that oil extracted from seeds of *Anethum graveolens* plant exhibited significant antimicrobial potency against used microbial strains (*Aspergillus parasiticus*, Standard: Itraconazole) [28]. Further extracted oil from Anethum graveolens showed various other biological potencies, such as diuretic [29], antidiabetic [30], and analgesic [31] potencies. Acetone extract and extracted oil exhibited good antimicrobial potency against used strains compared with standard. The observed activity due to the presence of coumarin, limonene, and carvone may be responsible [32–34] **Fig. 3.**

FIG. 3: SOXHLET EXTRACTION APPARATUS, OIL AND ANTIMICROBIAL POTENCY

Analgesic and Anti-inflammatory Effects: The hydroalcoholic extract exhibited good antiinflammatory activity in rats. The extracted oil and diclofenac gel exhibited excellent anti-inflammatory activity against rats compared to standard.

The organic extract (ethanol) of the fruits showed good activity compared with standard [35-37]. Racz-Kotilla E *et al.* 1995. Observed that the water extract of the fruit and oil exhibited excellent potency in mice by using the hot plate method [38].

Other Observed Effects: *Anethum graveolens plant* seed extract exhibited excellent effect in the gastrointestinal system observed in mice, and it reduces acidity and content of acid. The crude extract of *Anethum graveolens* showed good anti-hypercholesterol and anti-hyperlipidaemic potency. The powder and oil of the plant also showed good hypolipidaemic potency in rats [39–49].

Contraindications and Adverse Effects: Chui A M *et al.* 2000 & Nath D *et al.* 1992 reported that some rarely it exhibits allergic effects, sometimes swelling in tongue & throat. Further, it is advised to not used during pregnancy time, respectively [50-53].

Effects on Reproductive System: The *Anethum graveolens* plant aqueous and organic (ethanol) extract showed excellent potency observed in female rats. Results showed that both extracts exhibited good effects on reproductive systems [54–58].

Antioxidant Activity: The essential oil isolated from the plant *Anethum graveolens* exhibited excellent antioxidant activity compared with standard [59-60].

Isolated Molecules of *Anethum graveolens:* Hanan Y. Aati *et al.* (2022) reported the various molecules isolated from the seed, flower, leaves, and stem of *Anethum graveolens* are listed below **Fig. 4**.

From our group, different synthetic, natural product and their biological activities recent updates may be useful for the new researcher in designing new active drugs [61–82].

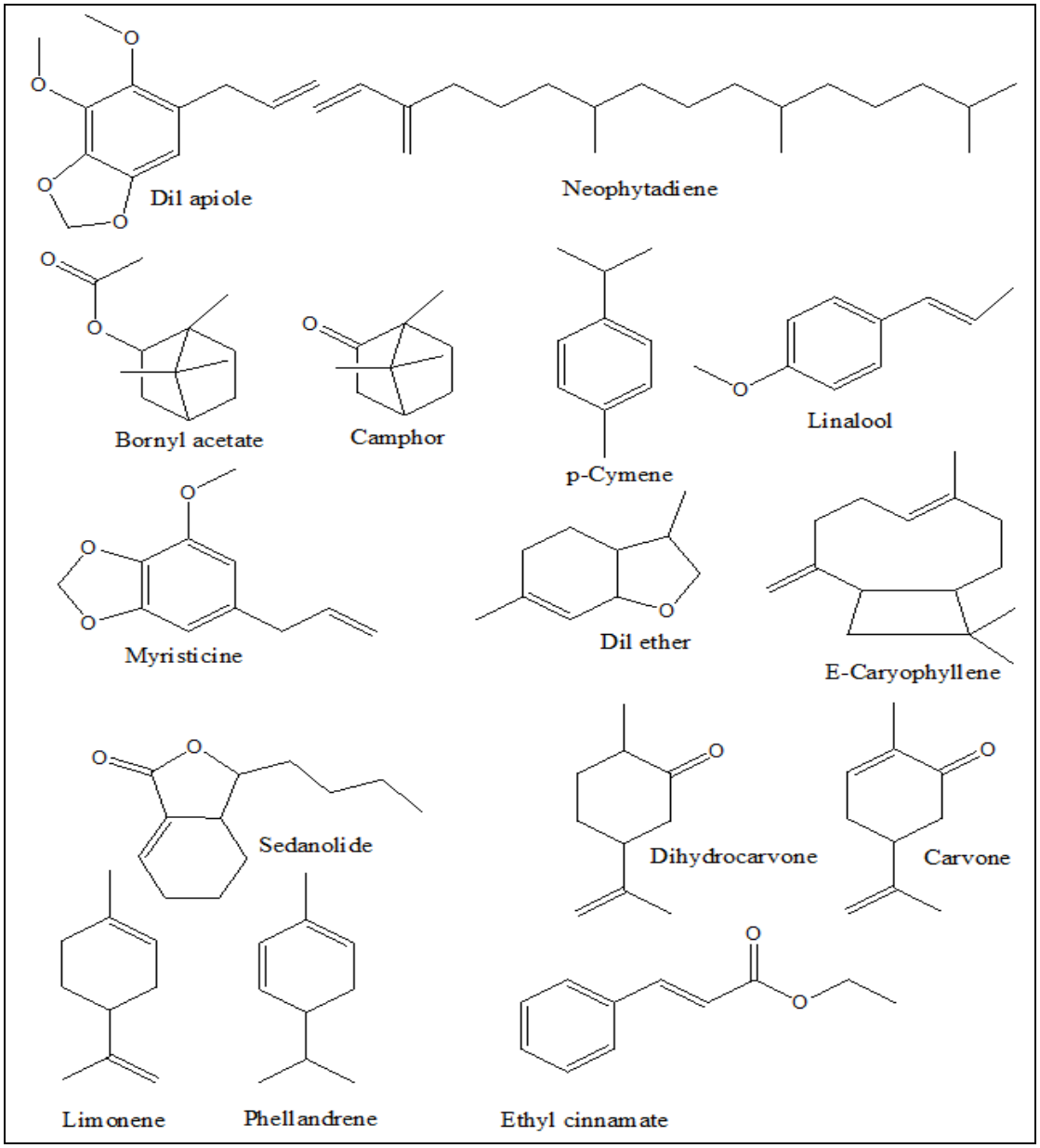

FIG. 4: THE VARIOUS MOLECULES ISOLATED FROM SEED, FLOWER, LEAVES AND STEM OF *ANETHUM GRAVEOLENS*

CONCLUSION: The leaves and seeds of the *Anethum graveolens* plant are mainly used for traditional health treatments like diuretics and stomach disorders. Various observations reveal that the whole plant has medicinal applications such as antidepressant, analgesic, antiproliferative, antimicrobial, anti-inflammatory, analgesic, antioxidant activity, effects on gastrointestinal system, hyperlipidaemic effects, contraindications and adverse effects, and effects on reproductive system. Further, it is also used to prevent food spoilage or contamination. In the food industry, also used for flavoring foods. The important isolated molecules reported are carvone, dihydrocarvone, limonene, cymen, carvacrol phellandrene, coumarins, flavonoids, phenolic acids, and steroids.

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THE NEUROBIOLOGY OF OVEREATING: DOPAMINE'S ROLE IN OBESITY

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ABSTRACT: Today, obesity has become a global pandemic affecting billions of people worldwide. It is associated with increased risks of various diseases, including cardiovascular and musculoskeletal diseases, psychiatric disorders, cancer, and diabetes, making it a significant public health issue. Obesity has also been linked to an elevated risk of metabolic diseases and changes in brain structure and function. The body mass index (BMI) is widely used to determine excessive weight in relation to height and age. However, BMI may not be accurate for everyone, and BMI z-scores are employed when analyzing data on children and adolescents. The accumulation of excess body fat, which contributes to obesity, is attributed to an imbalance between energy intake and expenditure, controlled by the brain's central nervous system. Disturbances in the brain circuits that regulate energy balance can impact body weight and adiposity, often involving changes in neurotransmission, which may be addressed with CNS-targeting drugs. The pathogenesis of obesity is characterized by a chronic energy imbalance between excessive calorie intake and inadequate calorie expenditure, primarily driven by decreased physical activity. Hormones and peptides produced by the enteric nervous system, such as cholecystokinin, ghrelin, and leptin, influence hunger and fullness, while leptin, an adipocyte-produced hormone, regulates energy expenditure and food intake. In conclusion, Understanding the pathogenesis and physiological mechanisms underlying obesity is crucial for developing effective prevention and intervention strategies.

INTRODUCTION: Today, obesity has been a universal pandemic after affecting billions of people all over the world [1]. Obesity is linked with escalated risks of many diseases such as cardiovascular and musculoskeletal diseases, psychiatric disorders, cancer and diabetes that is a significant public health issue [2].

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Excessive number of deaths all over the world are due to obesity and overweight having obesity rates incomparable in many countries [3]. The widespread presence of obesity is now three times from last forty years [4].

Over 1.9 billion individuals aged 18 and older were overweight in 2016, with over 650 million of them being obese. These figures indicate that 39% of people over the age of 18 (39% men and 40% women) were overweight, while 13% of the adult population worldwide (11% men and 15% women) had obesity [5]. Obesity has been linked to an increased risk of metabolic diseases as well as changes in brain structure and function, according

to research [6]. One of the most used methods for determining excessive weight in relation to height and age is the body mass index (BMI). The World Health Organisation divides obesity into four categories based on BMI: underweight (BMI less than 18.5 kg/m2), normal weight (18.5 to 25 kg/m2), overweight (26 to 30 kg/m2), and obese (more than 30 kg/m2) [7]. BMI has traditionally been utilised in adults; however it is now also being used in children and the elderly. Nevertheless, using BMI as an indicator of overweight or obesity is not accurate for everyone. Because BMI changes with age and sex in this group, BMI z-scores are employed when analysing data on children and adolescents [8].

Although, obesity is a complex multifactorial disease, the accumulation of excess body fat is mathematically explained by an imbalance between energy intake and energy expenditure [9]. The brain's central nervous system (CNS) controls these two energy balance equation factors [10]. Abnormalities in the brain circuits that control energy balance have a significant impact on body weight and adiposity [11].

These changes are as complex as fat. However, most, if not all, of these disturbances cause changes in neurotransmission, which can be addressed or improved with CNS-targeting drugs. Obesity's aetiology and pharmacology point to a neurotransmitter problem [12]. The brain's capacity to integrate behavioural, endocrine, and autonomic responses via afferent and efferent channels from and to the brainstem and peripheral organs underlies the control of body weight. The hypothalamus, in particular, is responsible for this ability [13].

Pathogenesis of Obesity: A loss of equilibrium between food intake and energy utilisation leads to obesity [14]. A chronic energy imbalance between excessive calorie intake and inadequate calorie expenditure is the primary factor causing obesity [15]. Energy used up during physical exercise, maintaining essential bodily functions, and diet-induced thermogenesis are all included in energy expenditure. The idea that obesity is brought on by irregularities in metabolic energy expenditure and/or diet-induced thermogenesis has not been substantiated by published studies; instead, data shows that decreased physical activity may significantly contribute to body weight increase [16]. The sympathetic nervous system (SNS) is involved in maintaining homeostasis. Eating, particularly eating excessively carbohydrate, boosts SNS activity whereas fasting decreases it. Lipolysis in adipose tissue is innervated by and modulated by the SNS [17]. By directly affecting the metabolic status of adipose tissue, parasympathetic input has the potential to modulate the aetiology of obesity. The SNS and macrophages must interact in neuroimmune ways for the homeostasis of many tissues, including adipose tissue [18].

The vagus nerve links the brain and digestive system. More than 30 neurotransmitters are produced by the enteric nervous system; these peptides and hormones are released into the circulation, pass across the blood-brain barrier, and stimulate the central nervous system (CNS). Intestinal hormones, including as the peptides cholecystokinin, ghrelin, and leptin, which control the feelings of hunger and fullness, are produced upon ingestion as a result of the stomach's dilation. By blocking vagal signals and repressing the release of insulin, ghrelin increases appetite [19].

The effects on SNS activity are mediated by leptin and insulin. An adipocyte-produced hormone called leptin is increased in obesity. It is an adipokine that controls a variety of physiological processes including immunity, energy expenditure, and food intake [20]. Circulating leptin concentrations serve as a direct indicator of the amount of energy stored in adipose tissue, and they typically promote energy expenditure while lowering appetite [21].

Leptin binds to its receptor in the brain and exerts its effects *via* the neuroendocrine axis. Additionally, it lessens the hyperglycemia brought on by inadequate insulin [22]. Leptin signalling is compromised when obesity progresses, resulting in leptin resistance. Despite having high blood leptin levels in these situations, the hormone is unable to connect to its receptor and regulate physiological activity [23]. Leptin resistance, which inhibits leptin signalling and its subsequent physiological consequences, is also linked to obesity. Despite having high amounts of adipokine in the blood, leptin treatment is unsuccessful in obese individuals because they acquire leptin resistance.

As there are currently no recognised medications for this function, reducing leptin resistance is an attractive research field with promise for weight-loss treatment [24].

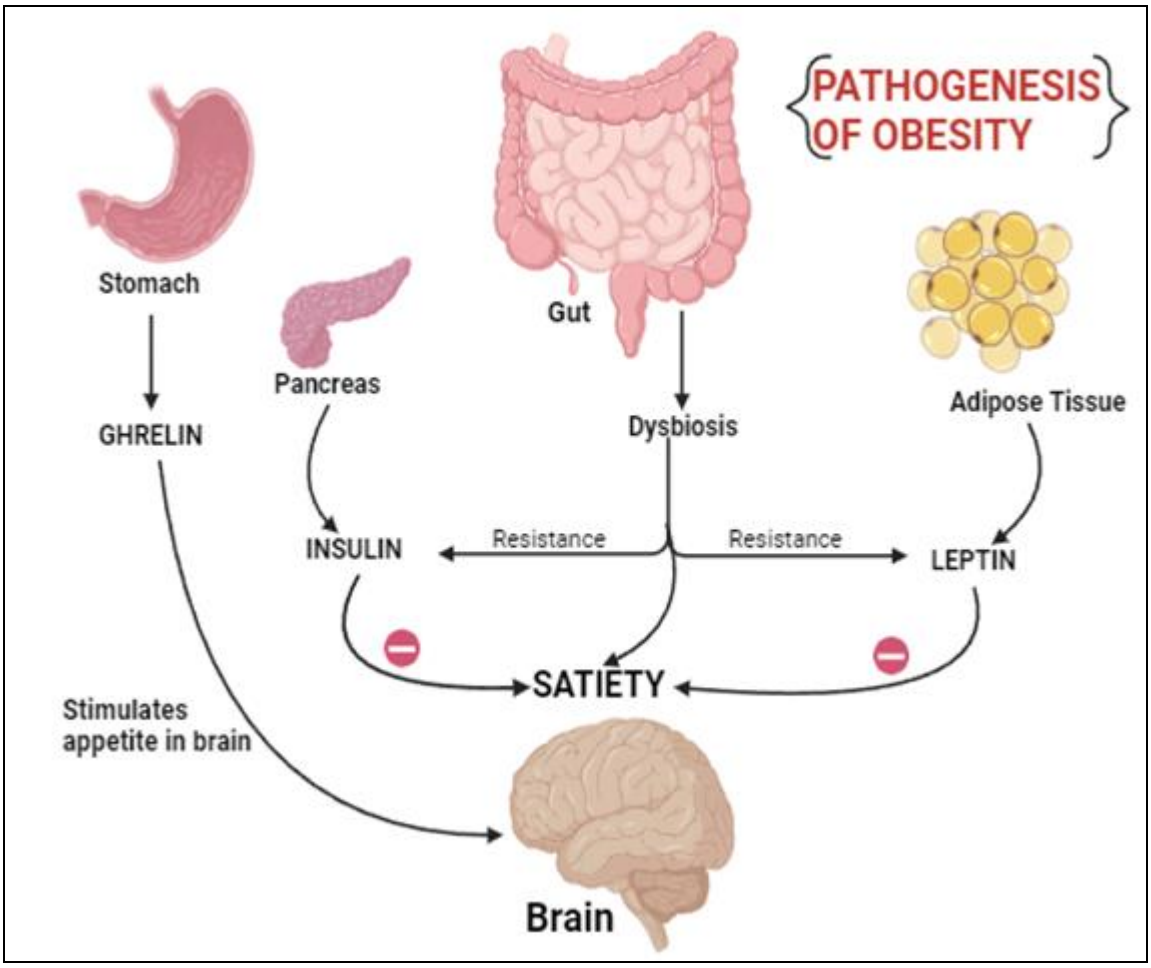

FIG. 1: PATHOGENESIS OF OBESITY

Gut Microbiota: The neurobiological control of eating behaviour is incredibly intricate and involves both motivational and energy homeostasis mechanisms [25-33]. Accordingly, controls that are homeostatic and non-homeostatic have been identified in the neural networks that govern eating behaviour [28, 33]. Homeostatic controls, which traditionally include the hypothalamus and brainstem nuclei, are a response to energy and other metabolic shortages [25, 26]. Hedonic and cognitive components of eating are handled by higher-order brain structures such as frontal cortical areas, mesolimbic circuits, and the hippocampus in non-homeostatic regulation [25, 29]. Additionally, the vagus nerve connects homeostatic and non-homeostatic feeding regulation by transmitting gastrointestinal hunger and satiety signals and modulating higher-order brain regions. The vagus nerve carries information in both directions between the brain and viscera, including the gastrointestinal tract [31-34]. The non-digestible dietary fibres are fermented by the gut microorganisms into short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, which are important for metabolism [35]. There was a correlation between obesity and an increase in the Firmicutes/Bacteroidetes ratio [36]. The microbiome's metabolites, which are produced when food is fermented, are crucial in controlling the metabolism of the host. In the colon, the gut bacteria transform bile acid into deoxycholic acid and lithocholic acid, which promote the release of the incretin hormones GLP-1 and insulin, hence increasing energy expenditure [37]. The chemical composition of the microbiome is also related to dietary choline metabolism. Microbiome-mediated trimethylamine-N-oxide (TMAO) synthesis from choline has been linked to metabolic and atherosclerotic diseases [38]. Several intestinal-resident bacteria facilitate the conversion of choline

to the intermediate trimethylamine [39]. The SCFAs generated by gut bacteria influence GLP-1 release, inhibit the inflammatory immune response in the gut, and are implicated in insulin signalling linked to fat formation [40-42]. Additional signs of obesity include indicators for inflammation and intestinal permeability [43]. These two issues are related because increased permeability makes it possible for bacterial byproducts to leak into the bloodstream and cause low-grade inflammation, which is a defining hallmark of obesity and insulin resistance [44].

Brain Pathways to Obesity: A forebrain corticolimbic appetitive network is coupled to autonomic hypothalamus and brainstem neural circuits via the brain regions responsible for the control of energy balance. The so-called anorexigenic pro-opiomelanocortin (POMC) neurons and the orexigenic agouti-related peptide (AgRP) neurons, which co-express neuropeptide Y (NPY), make up the melanocortin system in the arcuate nucleus of the hypothalamus [45]. With the third ventricle and median eminence nearby, these neurons are in a prime location for receiving a number of signals indicative of metabolic status. In fact, these neurons are able to recognise and react to a wide range of circulating hormonal and nutritional signals including fatty acids, insulin, glucagon-like peptide 1, leptin, glucose, and ghrelin [46]. As a result, fasting and other negative energy balance conditions activate AgRP/NPY neurons, whereas positive energy balance states activate POMC neurons [47]. Through their combined actions on the downstream cognate central melanocortin receptors melanocortin receptor 3 and melanocortin receptor 4 (MC4R)], these neurons differently control energy balance. The fact that POMC and MC4R mutations are the most prevalent types of monogenic obesitys confirms the significance of these circuits in controlling body weight [48].

The AgRP/NPY neurons, which are a part of the melanocortin system's opposing arm, control feeding through a variety of methods. These neurons coexpress the rapid inhibitory neurotransmitter GABA as well as AgRP, NPY, and NP [49]. AgRP's effects at MC4R are primarily what cause a rise in body weight and food intake after central injection of the substance [50].

Leptin: White adipose tissue is principally responsible for producing leptin, which is then released into the bloodstream. Higher plasma leptin levels are found in those who have more body fat, and these two variables are positively associated. However, as leptin levels drop by over two thirds following a week of caloric restriction, leptin production is closely linked to energy status [51]. Early research using obese animal models showed that leptin reduces food intake while increasing energy expenditure. Leptin deficiency causes animals to consume more food, expend less calories, and experience severe obesity [52]. However, only a tiny percentage of people are leptin deficient; the majority of people are leptin resistant, raising doubts about the effectiveness of leptin in treating obesity in people [53]. Leptin resistance in humans is evidence indicating people who are more likely to put on weight again after losing it had greater leptin levels, which is associated with poorer leptin sensitivity, than people who successfully maintain their weight [54].

Insulin: The integration of several peripheral metabolic signals depends on insulin. Insulin's ability to suppress NPY and activate POMC neurons makes this possible. Insulin is more readily present in the CNS because to insulin receptors in the blood-brain barrier. The entryway for insulin's entry into the central nervous system is the hypothalamus, particularly the arcuate nucleus, which is abundant in insulin receptors [55]. Mice missing insulin receptors in the CNS are insulin resistant, resulting in increased food intake and the development of diet-induced obesity. Insulin has a role in eating behaviours and consequent body weight maintenance [56].Circulating insulin levels are more strongly connected with visceral fat than subcutaneous fat, in contrast to leptin [57].

Ghrelin: The hunger hormone, ghrelin, decreases POMC neurons while activating NPY and AgRP neurons in the arcuate to increase appetite. Ghrelin counteracts leptin's suppression of NPY and AgRP neurons, while leptin counteracts ghrelin's stimulation of food intake, demonstrating how the two hormones interact [58]. Ghrelin therapy enhances hunger, food intake, and weight gain by acting on both the central and peripheral nervous systems [59]. Axons of POMC, NPY, and AgRP neurons that extend to the dorsomedial nucleus, lateral nucleus,

paraventricular nucleus, and ventromedial nucleus distribute the orexigenic signal to various areas of the hypothalamus and nonhypothalamic regions. Through its interaction with visceral vagal afferent neurons, ghrelin also affects hunger. Leptin and insulin both reduce the activation of NPY neurons caused by ghrelin [60]. Ghrelin levels are lower in obese people than in people of normal weight 194 and are lower in people with greater body fat, insulin, and leptin levels [61].

Obesty and Neuroinflammation: The buildup of glial cells in the brain and spinal cord (CNS) as a reaction to inflammation is known as neuroinflammation. This happens when proinflammatory cytokines (including IL-1 and TNF), cytotoxic substances, and reactive oxygen species (ROS) are secreted by activated astrocytes and microglia as soon as there is damage, which results in neuronal death [59]. Anatomical anomalies occurs in the amount of grey matter in obese people. When obesity is present, there is a continuous decrease in grey matter in the control areas of the inferior frontal gyri, right insula, left and right precentral gyri, left middle frontal gyrus, left middle temporal gyrus, left amygdala, and left cerebellar hemisphere. Nonetheless, an increase in the amount of grey matter was seen in the left inferior occipital gyrus, left middle frontal gyrus, and left cuneus in the examined studies [62]. A greater body mass index is linked to a reduction in several white matter areas, such as the superior and inferior longitudinal fascicles, corpus callosum, uncinate fascicle, internal capsule, corticospinal tract, inferior front-occipital fascicle, corpus callosum and cingulum (cingulate gyrus and hippocampus). Local alterations in the white matter fibre tracts linked to elevated body mass index (BMI) provide a connection between the prefrontal and limbic areas, perhaps elucidating the heightened likelihood of cognitive decline and dementia in older adults with obesity [63].

When comparing the diameters of the bilateral caudate with the bilateral thalamus, putamen, and globus pallidus, people who are obese have larger sizes than those who are normal weight [64]. The brain area known as the hippocampus, which controls memory and cognition, is frequently linked to obesity-related cognitive decline. Higher BMI (>30 kg/m2) has been linked in human studies to decreases in white matter integrity and grey matter volume in the hippocampus and other brain regions, underscoring the harmful consequences of obesity on brain structure [65]. Mechanisms *via* which obesity and a bad diet affect cognitive performance.

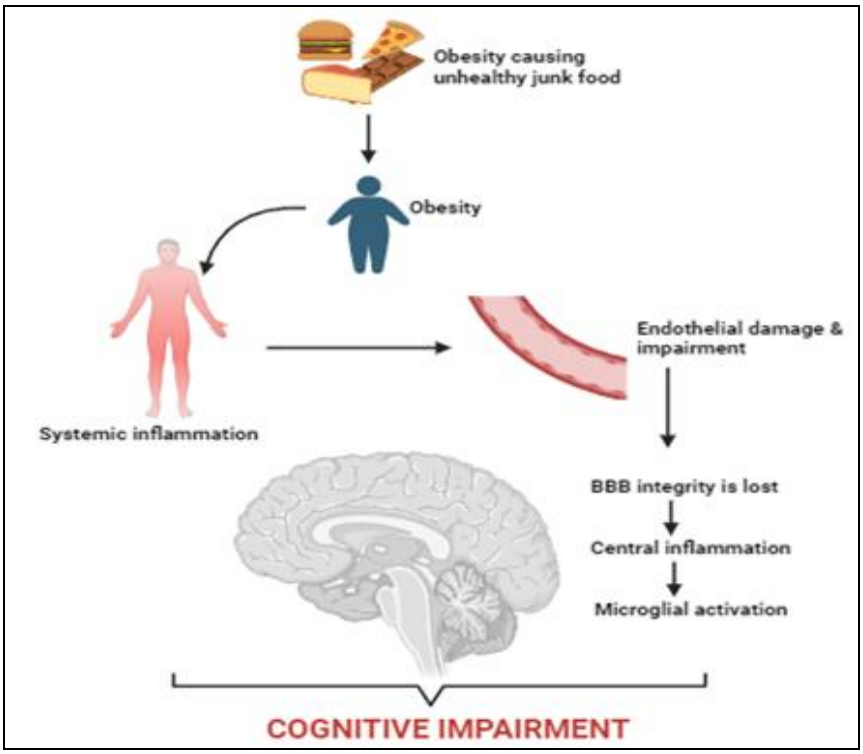

FIG. 2: EFFECT OF BAD FOOD ON COGNITIVE IMPAIRMENT

Obesity and/or poor nutrition leads to low-grade systemic inflammation that compromises the blood-brain barrier, causes central inflammation, activates microglia, and expresses pro-inflammatory proteins. These events cause synaptic remodelling, neuronal death, and decreased neurogenesis. Cognitive impairment is also associated with metabolic dysfunction, insulin resistance, development of white adipose tissue, and changes in the gut flora brought on by obesity. When neurotransmitter systems, including the glutamatergic, cholinergic, and dopaminergic systems, are disrupted, acetylcholine and dopamine levels drop and glutamate signalling becomes dysfunctional. These factors further impair memory, learning, and cognition, ultimately resulting in cognitive impairments [66].

More than 100 identified neurotransmitters are members of a large family of chemical messengers that are involved in synaptic transmission and that control physiological processes in the central and peripheral nervous systems [67]. The most researched neurotransmitters include glutamate, acetylcholine, norepinephrine, serotonin, gamma-aminobutyric acid (GABA), dopamine, and serotonin because they have therapeutic significance.

Serotonin: The primary mechanisms controlling feeding action are hedonic and homeostatic systems. The brainstem and hypothalamus are the main areas of the homeostatic system [68]. Other neurotransmitters are also involved in hedonic signalling, but dopamine and serotonin play major roles in it [69-70]. Serotonin, also known as hydroxy tryptamine, or 5-HT, is mostly found in the GI tract, platelets, and the serotoninergic neuronal network of the central nervous system. Serotonin functions as a peripheral hormone in addition to a neurotransmitter. Nonetheless, the intestinal mucosa's enterochromaffin (EC) cells produce the majority of the 5-HT. The human gut is the biggest endocrine organ, producing over 95% of all serotonin [71].

The reward pathway sometimes refers to the mesolimbic system, which includes the VTA, the nucleus accumbens (NAc) of the ventral striatum, and the CeA. It has also been suggested that these areas participate in the interplay between hedonic and homeostatic control of food intake [72].

An excess of energy intake over energy expenditure leads to obesity. As a result, it has been hypothesised that eating above one's needs for energy may be facilitated by reduced homeostatic inhibition and/or greater hedonic desire. Those who are chronically overweight or obese may have disrupted eating behaviour as a result of disruptions in serotonergic signalling, as this signalling plays a crucial role in regulating food intake. Indeed, evidence from several research suggests that obesity-related disruptions in serotonergic signalling occur in both humans and animals [73-74].

The human central serotonin system cannot be directly studied *in-vivo*. Serotonin and its metabolites in cerebrospinal fluid (CSF), postmortem immunohistochemistry of brain tissue, and molecular neuroimaging methods like positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have all been used to evaluate alterations in serotonergic signalling linked to obesity in humans [75]. The infundibular nucleus, which is comparable to the ARC in rats, showed lower levels of SERT protein in the post-mortem hypothalamus tissue of overweight/obesity-affected humans [76].

Serotonin (5-HT) has been linked to abnormal signalling in animal models of obesity and is implicated in the control of hunger [77-78]. The findings that, over a 4-week hypocaloric diet, thalamic SERT rose when the majority of daily calories were consumed during breakfast and fell when the majority of daily calories were received during supper suggest that meal time plays a role [79]. According to these research, serotonergic signalling alterations may arise early in the overindulgence in food that occurs in humans, potentially playing a role in the development and/or maintenance of obesity.

In order to manage food intake, the central 5-HT system is essential. Research from the 1970s was actually the first to demonstrate that in rodents, loss of brain 5-HT due to central infusion of 5,7-dihydroxytryptamine, a neurotoxin that specifically kills serotonergic neurons, or p-chlorophenyl alanine, an inhibitor of tryptophan hydroxylase, the rate-limiting enzyme in the biosynthesis of 5-HT, causes hyperphagia and obesity.

Medication that affects the central 5-HT system, such as locaserin, is effective in encouraging weight reduction [80-82]. The activation of central serotonergic transmission emerged as a treatment target for obesity well over ten years ago, based on the clear involvement of serotonergic transmission in eating habits and translational studies showing diminished serotonergic transmission in human obesity. Fenfluramine, sibutramine, and subsequently dexfenfluramine were all effectively marketed as therapies for obesity [83].

Dopamine: Molecular imaging studies have shown structural dopamine abnormalities in human obesity, namely in the area of dopamine release and availability of the D2/D3 receptor. However, dopamine synthesis capacity and dopamine reuptake transporters have also been studied [84]. The production and release of DA are regulated by steroid hormones, insulin, leptin, and other peripheral peptides [85]. It seems that DA is connected to the control of food intake on both a short-term (individual meals) and long-term (hunger) time scale [86].

There are five distinct subtypes of DA receptors, which may be divided into D1- (D1, D3) and D2- (D2, D4 and D5) similar subtypes. The regulation of eating behaviour is significantly influenced by both D1- and D2-like receptors. Reduced meal size through shorter eating sessions is the primary outcome of satiety signals, which are facilitated by DA's actions on D1 receptors. The key relationship between DA and D2 receptors is feeding rate. By shortening the length and pace of eating, a combination of DA agonists, such apomorphine, lowers appetite [87].

The gene that codes for the D2 receptors has received the majority of attention in human genetic research on the role of the DA system in obesity. Research conducted on laboratory animals has demonstrated that DA agonists normalised body weight in genetically obese mice (ob/ob) [88]. Human studies have shown a higher prevalence ofthe Taq I A allele for the D2 receptors in obese individuals [89]. Variants of the D2 receptor gene and the human obesity (ob) gene have been investigated in connection to obesity. When combined, these two polymorphisms explain around 20% of the variation in body mass index (BMI, which is calculated by dividing weight in kilogrammes by height in metres), especially in younger women [90]. The Taq I A allele's correlation with less D2 receptors implies that fat people carrying the A1 allele could use food to raise their DA stimulation to a more tolerable level. This is in line with research showing decreased DA metabolite concentrations in cerebral fluid in bulimic individuals who have frequent binge episodes [91].

According to brain imaging studies on obese patients, there was less binding of the tracer [11C] raclopride, which is selective for D2 and D3 receptors, in the striatum of obese subjects compared to controls. This suggests that the availability of D2/D3 receptors is downregulated in obesity. Comparing overweight and obese individuals (BMI > 27 kg/m2) to controls, similar results were found [92-93]. Results on differences in sex and gender in DA release are likewise conflicting. Female controls in a [123I] iodobenzamide SPECT scan responded to amphetamine with considerable DA release, while extreme obese women did not exhibit any meaningful change from baseline [94].

CONCLUSION: Obesity is a global health issue that affects billions of people worldwide, with obesity rates three times higher than in the last forty years. Obesity accumulation is mathematically explained by an imbalance between energy intake and energy expenditure, which is controlled by the brain's central nervous system (CNS). The pathogenesis of obesity involves a loss of equilibrium between food intake and energy utilization. A chronic energy imbalance between excessive calorie intake and inadequate calorie expenditure is the primary factor causing obesity. The sympathetic nervous system (SNS) is involved in maintaining homeostasis, and parasympathetic input has the potential to modulate the aetiology of obesity. The vagus nerve links the brain and digestive system, producing over 30 neurotransmitters that stimulate the CNS.

The gut microbiome ferments non-digestible dietary fibers into short-chain fatty acids (SCFAs), which are important for metabolism. The chemical composition of the microbiome is also related to dietary choline metabolism, and the SCFAs generated by gut bacteria influence GLP-1 release,

inhibit the inflammatory immune response in the gut, and are implicated in insulin signaling linked to fat formation. Inflammation and intestinal permeability are indicators of obesity, as increased permeability allows bacterial by products to leak into the bloodstream and cause low-grade inflammation, a hallmark of obesity and insulin resistance.

Obesity is a complex condition influenced by various factors in the brain. The melanocortin system, composed of anorexigenic pro-opiomelanocortin (POMC) neurons and orexigenic agouti-related peptide (AgRP) neurons, plays a crucial role in controlling energy balance. These neurons are located near the third ventricle and median eminence, and can recognize and react to various hormonal and nutritional signals. Fasting and other negative energy balance conditions activate AgRP/NPY neurons, while positive energy balance states activate POMC neurons. AgRP/NPY neurons control feeding through GABA, NPY, and NP. Leptin, a hormone produced by white adipose tissue, is closely linked to energy status and can reduce food intake while increasing energy expenditure. Insulin, a hormone that regulates peripheral metabolic signals, is more readily present in the central nervous system due to its blood-brain barrier receptors. Ghrelin, a hunger hormone, decreases POMC neurons and activates NPY and AgRP neurons in the arcuate to increase appetite. Ghrelin therapy enhances hunger, food intake, and weight gain by acting on both the central and peripheral nervous systems.

Obesity and neuroinflammation are linked to the buildup of glial cells in the brain and spinal cord, which results in neuronal death. Obesity leads to a decrease in grey matter in control areas such as the inferior frontal gyri, right insula, left and right precentral gyri, left middle frontal gyrus, left middle temporal gyrus, left amygdala, and left cerebellar hemisphere, while an increase in grey matter is seen in the left inferior occipital gyrus, left middle frontal gyrus, and left cuneus. Obesity also leads to alterations in white matter areas, such as the superior and inferior longitudinal fascicles, corpus callosum, uncinate fascicle, internal capsule, corticospinal tract, inferior front-occipital fascicle, corpus callosum, and cingulum. More than 100 identified neurotransmitters are involved in synaptic transmission and control physiological processes in the central and peripheral nervous systems. The reward pathway, which includes the VTA, the nucleus accumbens (NAc) of the ventral striatum, and the CeA, participates in the interplay between hedonic and homeostatic control of food intake. Obesity-related disruptions in serotonergic signalling occur in both humans and animals.

Molecular imaging studies have shown structural dopamine abnormalities in human obesity, specifically in the area of dopamine release and availability of the D2/D3 receptor. Dopamine is connected to the control of food intake on both short-term and long-term time scales. There are five distinct subtypes of DA receptors, with the regulation of eating behaviour significantly influenced by both D1- and D2-like receptors. The key relationship between DA and D2 receptors is feeding rate, with a combination of DA agonists like apomorphine lowers appetite. The Taq I A allele, which codes for the D2 receptors, has been linked to obesity, with variations explaining around 20% of the variation in body mass index. Brain imaging studies on obese patients show less binding of the tracer [11C] raclopride, suggesting down-regulation of D2/D3 receptors in obesity.

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PI3KΓ: A KEY PLAYER IN CANCER SIGNALLING PATHWAYS AND THERAPEUTIC TARGET FOR CANCER TREATMENT

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ABSTRACT: Phosphoinositide 3-kinase gamma (PI3Kγ) plays a vital role in cell signaling pathways essential for various physiological processes, including cell growth, differentiation, and survival. Dysregulation of PI3K signaling is implicated in the development and progression of several cancers. Activation of PI3K leads to the phosphorylation of critical proteins such as protein kinase B (PKB), ribosomal protein S6 kinase (RSK), and extracellular signal-regulated kinases 1 and 2 (ERK1/2), facilitated by the presence of phosphatidylinositol 3,4,5-triphosphate (PIP3). PI3K is involved in regulating immune responses, including thymocyte growth, neutrophil migration, and T cell activation. Numerous malignancies, including melanoma, lung cancer, prostate cancer, and breast cancer, have been linked to PI3K activity. For instance, PI3K activation is known to enhance breast cancer cell migration and invasion by stimulating the Akt/mTOR signaling pathway. Structurally, PI3Kγ consists of a catalytic subunit (P110γ) and regulatory subunits that modulate its activity. The P110γ domain architecture includes a C2 domain, helical domain, Ras-binding domain, and catalytic domain, which are critical for its function. The ATP binding pocket of P110γ is organized into distinct regions that influence substrate affinity and interactions, providing potential targets for inhibitor design.The PI3K pathway is activated through a multi-step process involving G protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs), resulting in the conversion of phosphatidylinositol (4,5)-bisphosphate (PIP2) to PIP3. This activation is tightly regulated by the phosphatase PTEN, which dephosphorylates PIP3 back to PIP2. PI3Kγ also influences cancer stem cell dynamics and immune modulation in the tumor microenvironment, presenting opportunities for novel therapeutic strategies.

INTRODUCTION: The enzyme PI3K, also known as phosphoinositide 3-kinase gamma, is crucial for cell signalling pathways that are involved in several physiological activities, including cell development, cell differentiation, and proliferation, and survival.

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Many forms of cancer are known to arise and advance because of PI3K signalling dysregulation [1]. The phosphorylation of protein kinase B (PKB), ribosomal protein S6 kinase (RSK), and extracellular signal-regulated kinases 1 and 2 (ERK1/2) is one of the signalling pathways that are activated in response to activating a GPCR. Presence of phosphatidylinositol 3,4,5-triphosphate (PIP3) makes this activation possible. which is connected to via PI3K. As a result, PI3K controls the growth of thymocytes, neutrophil migration, oxidative burst, and T cell activation. According to studies, many malignancies, including melanoma,

lung cancer, prostate tumors, & breast cancer, have been linked to PI3K. For instance, it's been demonstrated that PI3K activates the Akt/mTOR signalling, enhancing breast cancer cell invasion and migration [2]. PI3K has been discovered to control androgen receptor signalling and support cancer cell survival and proliferation in prostate cancer.PI3Kγ has been demonstrated to support tumour development and treatment resistance in lung cancer. By stimulating the Akt signalling pathway in melanoma, PI3Kγhas been demonstrated to improve the survival and multiplication of cancer cells.

Although p110 γ isoform is activated by both the Ras and GPCR pathways, current research has revealed a complicated interplay between these pathways. Reduced signalling downstream of GPCRs in neutrophils is the result of mutations in p110 γ that inhibit binding to Ras [3].

The PIK3CG gene produces the phosphoinositide 3-kinase gamma (PI3Kγ) enzyme, which belongs to the class I PI3K family. It is a lipid kinase that catalyses the production of second messenger molecules by phosphorylating phospha-tidylinositol's 3'-hydroxyl group on the inositol ring (PIs), which in turn activates signalling pathways that are crucial for cell growth, survival, and metabolism.

PI3Kγ Structure: The regulatory adaptor subunits p87/84 or p101, together with the catalytic subunit P110γ, make up the heterodimeric form of PI3Kγ. The catalytic P110γ has four domains formed from the residues 114 to 1102 namely, this includes the C2 domain, helical domain, Ras-binding domain, and catalytic. C2 domain consists of amino acid residues 357 to 522 responsible for the interaction with the membranes. RBD is formed from the residues 220 to 311 flanking next to the catalytic domain of P110γ and is known to activate the enzyme by the allosteric site mechanism. The function of helical domain containing residues from 547 to 725 is not interpreted till date. p110γ's catalytic domain comprised of amino acid residues from 726 to 1092 of which residues 726 to 883 accounts for the N lobe and the rest makes up the C-Terminal connected by a loop to the former lobe that represents the innate border of the ATP binding pocket. This structural representation is somewhat like that of numerous kinases hence making it difficult for the development of specific inhibitors of various isoforms [4].

ATP Binding Pocket: The ATP binding pocket is divided into four regions - hydrophobic region II , Hinge zone, specificity region, affinity pocket. These regions classified depending upon their affinity for the substrate binding. In the hinge region of p110γ, spanning from the N to C terminals. Adenine ring facilitates two H-bonds with Val882 & Glu880. Above and below of the ATP binding site, hydrophobic amino acid- Ile879, Ile831, lle963 & Phe961 encloses the adenine ring. The P loop interacts with the phosphate region of ATP represented by the amino acids from 803 to 811. The ribose ring faces hydrophobic region II and lacks every interaction with the protein. Three hydrogen bonds are facilitated between residues - Ser806, Asn951, Lys833 and the triphosphates of ATP [5].

The PI3Kγ Pathway: The PI3K pathway is functionally important, and it is activated in a multistep process. Activated G protein Coupled receptors and RTKs stimulate class 1 PI3Ks that are coupled to their regulatory subunits or adapter molecules. Upon activation, PI3K catalyses the conversion of phosphatidylinositol (3,4)-bisphosphate (PIP2) to phosphatidylinositol (3,4,5)-trisphosphate through its catalytic domain. The PTEN (Phosphate and tensin Homolog) dephosphorylated PIP3 to PIP2 and hence regulated the PI3K pathway. At the plasma membrane, The Akt binds to PIP3 and gets activated which triggers the beginning of numerous signaling pathway responsible for translation, cell proliferation, cell survival and apoptosis and so on [6].

Formation of cancer, growth of tumours, metastasis, and cancer recurrence are all significantly influenced by cancer stem cells (CSCs). Using mouse induced pluripotent stem cells (miPSCs) exposed to conditioned medium (CM) made from cancer cells, researchers have effectively created a model of CSCs. During this conversion process, the PI3K-Akt and EGFR signalling pathways are seen to be activated. Studies done in vivo and in vitro have revealed that inhibitors of these pathways, in particular PI3K inhibitors, significantly reduce the capacity of cells

to grow, replicate, move, and invade. These results imply that future treatment strategies against CSCs may involve targeting these pathways [7].

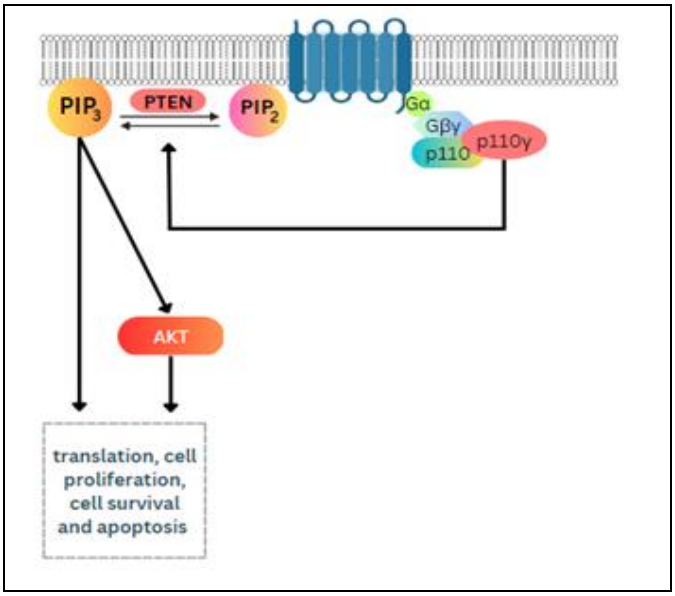

FIG. 1: ILLUSTRATION OF THE PI3KΓ SIGNALING PATHWAY

In addition, the ERK activation downstream of PI3K-γ is required for the parasite-induced, reactive oxygen species-dependent netosis.The release of parasitic neutrophil extracellular traps is greatly decreased by pharmacologically inhibiting protein kinase C [8].

PI3Kγ as Therapeutic Target:

PI3Kγ in Hematologic Malignancies: Because PI3K isoforms have a great deal in common in terms of sequence homology, it is challenging to inhibit PI3K specifically to reduce inflammation and immunosuppression in the cancer microenvironment. IC_{50} = 0.064 M upon the THP-1 cell line revealed >700-fold isoform selectivity for PI3K by a novel family of potent PI3K inhibitors with high isoform selectivity produced by divergent projection of substituents into ATP binding site pockets. Increased -selectivity is achieved by inhibitors with bicyclic hinge-binding motifs and the capacity to make numerous hydrogen bonds to the PI3Kγ hinge region [9]. Because molecular switch PI3K γ regulates immune suppression, its blockage regulates the activation of macrophages and changes them into immunological responses which leads to anticancer activity. Although the AS-605 PI3K inhibitor effectively biochemically inhibited PI3K-Akt signalling in T-ALL cell lines, it had no detectable impact in preclinical studies utilising animals that had T-ALL cell transplants or *in-vitro*. Although PI3K inhibition alone does not seem to be adequate for T-ALL therapy, it may be a beneficial therapeutic approach in other clinical settings, such as cancer immune therapy [10]. Treatment options for T-cell acute lymphoblastic leukaemia (T-ALL) are few. Ras signalling is common in T-ALL, and PI3K inhibitors appear to be effective. However, in T-ALL cell lines, single-agent therapy is ineffective in causing cell death. Even though the combination of pan-PI3K and PI3K-specific inhibitors exhibits strong synergistic effect in vitro, preclinical testing in a cancer model called T-ALL that replicates genetic heterogeneity has been unsuccessful. For logical design, combination treatment may need techniques for resolving biochemical signals in different cell populations.

Macrophage PI3Kγ regulates immune response in inflammation and cancer, with therapeutic potential in controlling immune suppression. Inhibiting PI3Kγ promotes immunostimulant, restoring T cell activation and synergizing with checkpoint inhibitors for tumor regression and improved survival. Targeting PI3Kγ-mediated gene expression predicts survival in cancer patients [11]. Duvelisib works by inhibiting PI3Kδ/γ, which is also used to treat relapsed/refractory chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma tumours (SLL). Duvelisib boosted autophagy inhibition and according to dose decreased lung fibroblast activation by inhibiting PI3K, Akt, and mTOR phosphorylation. Findings show that Duvelisib can lower the pulmonary fibrosis immunological severity and provide potential drugs for the therapy [12].

JN-PK1 inhibits a few cancer cell lines, especially those connected to blood cancer. Cell-free enzymatic tests show that this enzyme selectively targets PI3K and spares other PI3K isoforms at low micromolar doses. JN-PK1's interactions with the PI3K system's Ile881, Ile963, and Ile879 residues were important and were discovered by *in-silico* study. Additionally, the stable placement of JN-PK1 inside the active site may be impacted by an H-bond that forms between one of the acetyl groups in JN-PK1 and Lys833 in PI3K as well as steric hindrance brought on by Lys833's side chain [13].

PI3K-γ in Diet-induced Obesity and Insulin Resistance: PI3K-γ enzyme has been demonstrated to reduce conventional macrophage activation by promoting the production of immunosuppressive genes during acute inflammation. PI3K-γ has a large impact on both obesities brought on by diet and insulin resistance. In an effort to understand the behind molecular mechanisms, researchers found that the action of PI3K-γ in the control of adiposity, which was brought on by PI3K-γ function in a nonhematopoietic cell type, was largely dependent on its role in the regulation of inflammation and insulin resistance. Leukocyte PI3K-γ activity is nevertheless necessary for efficient neutrophil attraction to adipose tissue. PI3K-γ activity in leukocytes encourages early-onset insulin resistance and adipose tissue inflammation during obesity [14].

Chronic Rejection is Defended against PI3K Deletion: In clinical solid organ transplants, chronic rejection continues to be a significant factor in graft failure [15]. AA heart transplant model using class II MHC-mismatched hearts (specifically B6.H-2bm12 donor hearts into C57BL/6 recipients) to examine the role of PI3K inhibition in chronic rejection. When compared to WT receivers, heart allografts retrieved from PI3Kγ$^{-/-}$ recipients on day 28 had considerably less infiltration, fibrosis, and intimamedial thickness [16].

PI3Kγ Inhibition to Immune Suppression and Promotes Cancer Regression: PI3Kγ thought Akt and mTOR activation inhibits NFκB activation and C/EBPβ activation promotes immune suppression. Selectively inhibiting PI3Kγ reverses the activity. PI3Kγ and checkpoint inhibitor therapy give synergistic effects that promote tumour regression and increases the survival of the mouse model [17].

PI3Kγ Subunit Responsible for Regression in Tumour: In MDA MB-231 cells, PI3K subunits were knocked down separately (p84, p101, and p110γ), which lowered the cell lines' in vitro migration. In SCID animals, p110c or p101 knockdown prevented lung colonisation, Akt phosphorylation, and apoptosis. Like this, the suppression in 4T1.2 murine epithelial carcinoma cells of subunits p101 and p110γ prevented lung colonisation, spontaneous metastasis, and development of the main tumour. In contrast, Akt phosphorylation and lung colonisation were increased in MDA MB-231 cells with p84 knockdown. These results mark the first time that the two regulatory subunits of PI3Kγ have distinct roles in developing cancer, and they show the same degree as p110γ can be inhibited *in-vivo* cancer growth and metastasis by p101 deletion [18].

PI3K in Breast Cancer: Vascular disrupting agents (VDAs) have emerged as promising cancer treatments. A new VDA called poly(l-glutamic acid)-combretastatin A4 conjugate (PLG-CA4) shows significant antitumor activity. However, PLG-CA4 can trigger immune responses that promote tumor growth. In this study, researchers discovered that inhibiting phosphoinositide 3-kinase gamma (PI3Kγ) reduces the immunosuppressive effects of PLG-CA4 treatment. By inhibiting PI3Kγ, the number of M2-like tumor-associated macrophages (TAMs) decreased, potentially enhancing the presence of cytotoxic T lymphocytes (CTLs). Furthermore, the combination of a PI3Kγ inhibitor with PLG-CA4 resulted in prolonged survival and improved therapeutic effects when combined with an immune checkpoint inhibitor. These findings highlight the potential of PI3Kγ inhibition to enhance the efficacy of VDAs and overcome immune resistance in tumors [19]. Studies have shown out of multiple mechanism of immune resistance myeloid cells plays major role in tumour immunity by high filtration of immune suppressive cells and Immune checkpoint blocking (ICB). Selective pharmacological blocking of PI3Kγ overexpresses in myeloid cells restores ICB sensitivity. Which results in tumour reduction without a direct attack on cancer cells [20].

Neointimal Formation and Phenotypic Modification of Vascular Smooth Muscle Cells: Through controlling the production of YAP and the activation of the transcription factor CREB, PI3Kγ governs the phenotypic modification of VSMCs. A novel treatment strategy to treat proliferative vascular disease may involve modulating PI3Kγ signaling on the local vascular wall [21].

Bone Cancer Pain: This study investigated the role of PI3Kγ/Akt in bone cancer pain (BCP). Researchers found that PI3K and pAkt were increased in astrocytes, spinal neurons, even a tiny portion of microglia in rats that had cancer cells

transplanted. Spinal PI3Kγ inhibition reduced pAkt up-regulation and repressed BCP behaviour. These findings suggest that PI3Kγ/Akt regulation may be a potent BCP treatment approach [22].

Combination Therapy: Oncolytic viruses (OVs) show promise in anticancer immunotherapy, but treatment resistance remains a challenge. Tumor-Associated Myeloid Cells (TAMCs) the anticancer action is diminished of oncolytic virus M1 (OVM) by inhibiting $CD8^+$ T cells. OVM-induced TAMCs infiltrate and strengthen their immunosuppressive phenotype via IL-6 activation of PI3K-γ/Akt axis. Targeting PI3K-γ improves OVM efficacy by relieving TAMC-mediated immunosuppression, and checkpoint antibodies eliminate solid tumours that are resistant to treatment and activate a durable antitumor immunological memory. OVM's antitumor activity is double-edged, and TAMC-mediated immunosuppression must be abolished for T cell-mediated antitumor activity to prevail [23].

Tumours of the Pancreas: Blocking PI3Kγ and the colony-stimulating factor-1 receptor (CSF-1R) together has a synergistic impact that increases the anti-tumor effect by increasing M1 tumor-associated macrophages (TAM), improving M2 TAM, and decreasing the migration by myeloid-derived suppressor cells (MDSCs) into the tumour. Dual blockage gives an approach to alternate therapy for pancreatic cancer [24].

In macrophages found in pancreatic ductal adenocarcinoma (PDAC), PI3Kγ is highly expressed In murine of PDAC, PI3Kγ inhibition slows tumour development and progression and increases survival. Inhibiting PI3K prevents fibroblast-induced pancreatic desmoplasia and tumour cell migration by increasing lymphocyte T CD8 recruitment and decreasing macrophage production of Platelet Derived Growth Factor-BB (PDGF-BB). These results imply that PI3Kγ targeting in macrophages may be a possible PDAC treatment approach [25] in tumor-associated B cells PI3Kγ was also found to be substantially elevated. The only PI3Kγ inhibitors in clinical development, IPI-549, is a cutting-edge strategy for enhancing the anti-tumor immune response. polymeric nanoparticles (NP) of encapsulated IPI-549 investigated for its efficacy in melanoma models and pancreatic cancer in mice. In both cases, IPI-549 NP dramatically reduced tumour development and increased host survival. IPI-549 NP therapy significantly reduced the tumour's+suppressive microenvironment of both plasma and cells repressive myeloid in the tumour. This way IPI-549 NP administration might be an effective treatment for Tumours of the pancreas and similar immune-suppressive malignancies [26].

Breast cancer-In this study using mice models of breast cancer, Nano-PI and -PD1 together produced long-lasting tumour remission and eradicated lung metastases. The use of Nano-PI increased medication delivery to lymph nodes and tumours, whereas the use of PTX and IPI-549 promoted macrophage repolarization. According to immune cell profiling, CD8+ and CD4+T cells, dendritic cells and B cells increased whereas T cell and regulatory T cellsfatigue decreased. According to this research, combining Nano-PI and -PD1 can change the immunological milieu in tumours and lymph nodes, leading to the long-term remission of mice with metastatic breast cancer. As a possibility for further development, this combination offers bright future promise [27].

To alter the tumour immunological microenvironment, a nanoregulator incorporating MnO_2 particle and small molecules IPI-549 is created. It alleviates hypoxia along with inhibits PI3Kγ on MDSCs, resulting in PD-L1 downregulation, TAMs polarization, enhanced infiltration of Tc and Th cells also suppressed Treg cells infiltration of gives adequate tumor immunotherapy. This nanoregulator also allows tumor-specific MRI and effectively inhibits metastasis and tumor re-growth in an animal study [28].

Colitis Associated Cancer: Recurring flare-ups of damage to tissue characterise a chronic inflammatory disease of the colon, ulcerative colitis. In people with susceptible genes, it is thought to be brought on by an aberrant immunological response to the intestinal microbes. Colorectal cancer can occur because of ulcerative colitis's chronic colon inflammation. Recent research has demonstrated that PI3K regulates the innate immune response in the gut and that deregulation of this pathway can lead to the onset of ulcerative colitis & colorectal cancer.

By regulating the actions of innate immune cells like macrophages, PI3K inhibition has been demonstrated to lessen colon inflammation & tumor development in a mouse model of ulcerative colitis [29].

Chemical Language Models: CLM-based bioactivity prediction was used to refine a virtual chemical library. CLM that has been fine-tuned using known PI3Kγ ligands. Experimentation verified computer-generated designs. There has been the discovery of a novel PI3Kγ ligand having sub-micromolar activity, showing scaffold-hopping potential.

Chemical synthesis and biological tests showed the ability to produce PI3Kγ ligands having medium to minimal nanomolar activity. In a medulloblastoma cell model, the most effective medications reduced PI3Kγ dependent Akt phosphorylation, indicating the potency of PI3K ligands in suppressing the PI3K/Akt pathway in cancer cells [30].

PI3K Signaling in PDAC: The decrease in tumour size brought on by p110 deficiency can be reversed by HFDs through compensatory increased levels of alternative p110 isoforms. Even though p110γ acts as a cell-autonomous malignancy promoter, systemic p110γ deficiency in the presence of a compromised exocrine pancreas can result in minor liver damage that can worsen in the presence of a high-fat diet. Additionally, this impairs the metabolism of lipids and glucose. These data suggest that PI3K pathway-targeting drugs may be underutilised for the treatment of Pancreatic ductal adenocarcinoma (PDAC) and may increase the risk of adverse effects, such as Non-Alcoholic fatty liver disease (NAFLD), particularly in the setting of obesity [31].

Clinical Trials Investigating PI3Kγ Inhibitors: Several clinical trials are currently underway to investigate the efficacy and safety of PI3Kγ inhibitors. These trials aim to explore the potential of targeting PI3Kγ for various medical conditions. The following table summarizes some of the ongoing clinical trials investigating PI3Kγ inhibitors, as listed on the clinicaltrials.gov website [32].

TABLE 1: CLINICAL TRIAL DATA ON PI3Kγ

Study Title	Conditions	Interventions	Phases
Safety and efficacy study of tenalisib (RP6530) in combination with pembrolizumab in relapsed or refractory CHL	Classical hodgkin lymphoma	Drug: tenalisib biological: pembrolizumab	Phase1
A study of duvelisib in combination with pembrolizumab in head and neck cancer	Head and neck squamous cell carcinoma	Drug: duvelisib biological: pembrolizumab	Phase1|phase2
A safety and efficacy study of duvelisib in relapsed/refractory follicular lymphoma	Follicular lymphoma	Drug: duvelisib	Phase2
Safety and efficacy study of a dual PI3K delta/gamma inhibitor in T-cell lymphoma	Lymphoma, T-cell, peripheral lymphoma, T-cell, cutaneous	Drug: RP6530	Phase1
Efficacy and safety of tenalisib (RP6530), a PI3K δ/γ and SIK3 inhibitor, in patients with locally advanced or metastatic breast cancer	Locally advanced breast cancer metastatic breast cancer	Drug: tenalisib drug: tenalisib	Phase2
Safety and efficacy of tenalisib (RP6530) in combination with romidepsin in patients with relapsed/refractory T-cell lymphoma	T cell lymphoma	Drug: tenalisib drug: romidepsin	Phase1|phase2
Window of opportunity study of IPI-549 in patients with locally advanced HPV+ and HPV- head and neck squamous cell carcinoma	Head and neck squamous cell carcinoma head and neck cancer head and neck carcinoma head and neck cancer stage IV head and neck cancer stage III HPV-related carcinoma HPV-related malignancy HPV-related squamous cell carcinoma	Drug: IPI-549	Phase 2
Efficacy and safety study of tenalisib (rp6530), a novel PI3Kδ/γ dual inhibitor in patients with relapsed/refractory indolent non-hodgkin's	Non hodgkin lymphoma	Drug: tenalisib	Phase 2

lymphoma (iNHL)			
A study of duvelisib in patients with relapsed or refractory peripheral t cell lymphoma (PTCL)	Peripheral t-cell lymphoma	Drug: duvelisib	Phase 2
Efficacy and safety of tenalisib (RP6530) in patients with relapsed/refractory chronic lymphocytic leukaemia (CLL)	Leukaemia, lymphocytic, chronic, B-cell	Drug: tenalisib	Phase 2

CONCLUSION: Inhibitors targeting the PI3K-Akt and EGFR signalling pathways show promise in inhibiting the growth, invasion and migration abilities of cancer stem cells (CSCs) and may be effective in future therapies. Selective inhibition of PI3Kγ has shown significant results in inhibiting cell proliferation and self-renewal. Additionally, PI3Kγ inhibition has been found to regulate immune suppression, activate macrophages, and promote anti-cancer activity. In various cancer types, including leukaemia and breast cancer, targeting PI3Kγ has shown potential in combination therapies and immune modulation.

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CURRENT AND FUTURE ADVANCEMENT OF FAST DISSOLVING ORAL THIN FILM

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Keywords:

Fast dissolving drug delivery system, Oral thin film, Superdistintegrants, Dissolution, Disintegration

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ABSTRACT: The development of fast-dissolving oral thin films has recently followed the progression of dosage forms from straightforward ordinary tablets and capsules to modified release tablets and capsules, oral disintegrating tablets, and wafers. A hydrophilic polymer used in fast-dissolving oral thin films quickly hydrates or adheres when applied on the tongue or in buccal cavity. These films melt or disintegrate in a matter of seconds, releasing the active ingredient without need for drinking or chewing. A drug-containing thin film with surface area of 5 to 20 cm2 is called an oral dissolving film. The maximum single dose of the drugs that can be loaded is 30 mg. As opposed to tablets, several pharmaceutical companies are now producing oral thin films that dissolve quickly. Films combine the benefits of liquid dosage forms with those of tablets, such as exact dose and simple administration (easy swallowing, rapid bioavailability). At the same time, it gives a general overview of crucial formulation design factors that have an impact on thin films, such as thin film design, anatomical and physiological constraints, choice of the best manufacturing processes, characterization techniques, and the physicochemical properties of drugs and polymers. Fast-dissolving oral thin films can be used for a variety of purposes, including sublingual and gastro-retentive delivery systems in addition to buccal fast-dissolving systems. Future uses might involve employing laminated multilayer films to combine incompatible active medicinal components into a single product.

INTRODUCTION: The oral route of medication administration is one of the most practical, economical, and favoured drug delivery methods. However, certain patients, particularly those who are young or elderly, have trouble swallowing or digesting various oral solid dose forms, such as tablets and hard gelatin capsules. They are unable to consume these dose forms due to their fear of choking.

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Numerous fast dissolving drug delivery systems (FDDDS) were developed to address this issue [1]. Drug administration through the buccal cavity is crucial. By giving the medication via the buccal route, issues such high first pass metabolism and drug degradation in the gastrointestinal environment can be avoided [2].

The development of fast-dissolving oral thin films has recently followed the progression of dosage forms from straightforward ordinary tablets and capsules to modified release tablets and capsules, oral disintegrating tablets, and wafers. A hydrophilic polymer used in fast-dissolving oral thin films quickly hydrates or adheres when applied on the tongue or in the buccal cavity. These films melt or disintegrate in a matter of seconds,

releasing the active ingredient without the need for drinking or chewing [3]. Due to the mucosa's extensive blood supply, medications are quickly absorbed and instantly bioavailability. Bypassing first pass metabolism leads to immediate bioavailability. They are therefore often created for medications with high first pass metabolism in order to achieve higher bioavailability. Despite being in its infancy, oral thin- film technology has a promising future because of patient compliance [4].

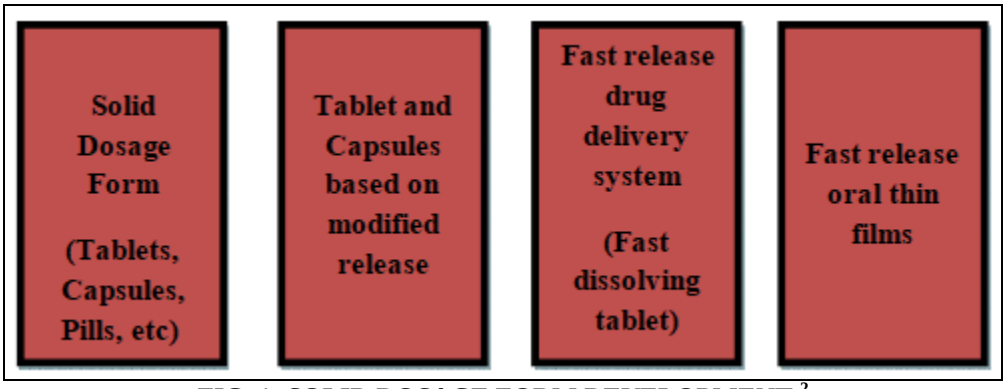

FIG. 1: SOLID DOSAGE FORM DEVELOPMENT [2]

Fast dissolving drug delivery systems are one such example that has recently begun to acquire popularity and acceptability with more customer choice due to its quick disintegration or dissolve and self-administration even without water or chewing. Fast dissolving medication delivery systems were originally developed in the late 1970s to help paediatric and elderly patients who had trouble swallowing tablets and capsules. Recent years have seen a rise in the importance of buccal medication delivery [5]. The use of polymeric films for buccal distribution, also known as mouth dissolving films, and other bio adhesive mucosal dosage forms, such as sticky tablets, gels, ointments, patches, and more recently, mouth dissolving films, have all been created. RDFs, or rapidly dissolving films, were first marketed as breath fresheners and personal care items like soap strips and dental care strips. Materials like strip-forming polymers, plasticizers, active pharmaceutical ingredients, sweeteners, saliva-stimulating agents, flavouring agents, colouring agents, stabilising and thickening agents, permeation enhancers, and superdisintegrants are used in the formulation of fast-dissolving buccal films. According to regulatory considerations, every excipient utilised in the creation of fast-dissolving films should be authorised for use in pharmaceutical dosage forms for oral administration [6-8].

Need for Formulating the Oral Thin Film: Children, the elderly, people who are bedridden, people who are emetic, and those who have CNS illnesses have trouble swallowing or digesting solid dose forms. Many of these individuals refuse to take solid dose forms because they are afraid of choking. Choking fears are common, even with ODTs, which can be dangerous. ODTs can be replaced by a fast- dissolving oral thin film drug delivery device. OTFs are immediately salivated upon placement on the tongue's tip or base. Because of this, OTFs quickly hydrate before dissolving or disintegrating to release the drug for local or systemic absorption. ODTs are brittle and might crack when being handled or transported. Consequently, quick dissolving oral thin film drug delivery devices are being created [9-11].

Features of Oral Thin Film [10]:

- Film should be thin and elegant.
- Available in various size and shapes.
- It should adhere to the oral cavity easily.
- Should processes fast disintegration without water.
- It should taste good.
- Drugs should be very moisture resistant and penetrate the oral mucosa.
- It should have appropriate tension resistance.
- It should be ionized in the oral cavity pH.

Advantages of Oral Thin Film [11-16]:

1. Convenient dosing.
2. No water needed.
3. No risk of chocking.
4. Taste masking.
5. Enhanced stability.
6. Improved patient compliance.
7. The drug enters the systemic circulation with reduced hepatic first pass effect.
8. Site specific and local action.
9. Availability of large surface area that leads to rapid disintegration and dissolution within oral cavity.
10. Bypasses the gastrointestinal tract and thus increasing bioavailability.
11. It provides more accurate dosage when compared to liquid dosage forms.
12. No need to measure, which is an important disadvantage in liquid dosage forms.

Disadvantages of Oral Thin Film [17-22]:

- Drugs with high dose cannot be incorporated into the film.
- Drugs which causes irritation to the mucosa cannot be administered.
- As it is fragile and must be protected from water, it requires special packaging.
- Dose uniformity is difficult to maintain.
- Only those active pharmaceutical ingredients having small dose can be incorporated.
- Since OTFs dissolve quickly, dose termination is impossible.
- OTFs are not official in any pharmacopoeia.

Types of Oral Thin Film [4]:
There are three types of Oral Thin Film:

1. Flash Release.
2. Mucoadhesive Melt Release.
3. Mucoadhesive Sustained Release.

Standard Composition of Oral Fast Dissolving Film: A drug-containing thin film with a surface area of 5 to 20 cm2 is called an oral dissolving film. The maximum single dose of the medications that can be loaded is 30 mg. All excipients employed in the formulation must be licenced for use in oral pharmaceutical dosage forms and be generally recognised as safe (i.e., GRAS-listed) from a regulatory standpoint [24-27].

A typical formulation contains the following ingredients:

1. Drug.
2. Film forming polymers.
3. Plasticizers.
4. Saliva stimulating agent.
5. Sweetening agent.
6. Flavouring agent.
7. Surfactant.
8. Colors, Filler.

TABLE 1: STANDARD COMPOSITION OF OTF [11-18]

Sr. no.	Category	Composition
1	Drug API	1-30 %
2	Film forming polymers	45-55 %
3	Plasticizers	0-20 %
4	Saliva sweetening agents	1-6 %
5	Sweetening agents	4-6 %
6	Flavoring agents	Q. S
7	Surfactant	Q. S
8	Colors and Filler	Q. S

Ideal Characteristics of APIs to be Incorporated into Fast Dissolving Oral Thin Films:

1. Low dose.
2. Palatability.
3. Small molecular weight.
4. Solubility and stability in saliva.

Some of suitable candidates for incorporation into thin film formulation are given in **Table 2.**

TABLE 2: SUITABLE DRUG CANDIDATE FOR OTF [1-8]

Sr. no.	Drug Candidate	BCS Class	Medicated Indications
1.	Glipizide	II	Anti-diabetic
2.	Donepizil	II	Anti-Alzheimer
3.	Famotidine	III	Antacid
4.	Ondansetron	II	Anti-emetic
5.	Loperamide	II	Anti-diarrheal
6.	Carvedilol	II	β-blocker
7.	Mirtazapine	II	Anti-depressant
8.	Indomethacin	II	NSAIDs
9.	Loratadine	II	Anti-histaminic

Film-forming Polymers used in OTFs: The choice of polymers, which relies on the quantity of films employed, is one of the most crucial and significant factors in the effective manufacture of oral films. A minimum of 45% polymer by weight must be present in the dry film, but 60%-65% polymer by weight is preferred to attain the desirable characteristics. To produce the necessary film qualities, polymers can be used alone or in combination. The film-forming polymers used must be water-soluble since OTFs are quickly dissolved and disseminated in the oral cavity. Additionally, the resulting films must be strong and damage-free throughout storage and transportation.

Properties of an Ideal Polymer for OTFs are the following [25-28]:

- The polymer used must be nontoxic and non-irritating.
- There should not be impurities.
- It must have enough wetting and spreading properties.
- It must have sufficient stress and tensile strength.
- It should be accessible and not too expensive.
- The shelf life should be reasonable.

Superdisintegrants used in OTFs: When Superdisintegrant are added to OTF formulations, the combined effects of swelling and water absorption result in fast disintegration. Due to their high water absorption, Superdisintegrant provide absorption and swelling, which speeds up disintegration and breakdown. Strong saliva contact is crucial for breakdown [2].

TABLE 3: ROLES OF POLYMER USED IN ORAL THIN FILM [1-5]

Sr. no.	Category	Composition	Examples
1	Film Forming Polymer	45-55 %	Carbohydrates, proteins, and cellulose derivatives, HPMC E3, E5 and E15 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan, carboxmethylcellulose cekol 30, polyvinylpyrollidone PVP K-90, pectin, gelatin, sodium, alginate, hdroxypropylcellulose, polyvinyl alcohol, maltodextrins
2	Plasticizers	0-20 %	Glycerin, PEG-400, 300, propylene glycol, malic acid, sorbitol, castor oil, triethyl citrate, tributyl citrate, and triacetin, etc.
3	Saliva Stimulant	1-6 %	Ascorbic acid, citric acid, lactic acid, tartaric acid, and malic acid
4	Sweeteners	4-6 %	Saccharin, cyclamate, and aspartame, Natural (sucrose, mannitol, sorbitol, dextrose, glucose, liquid glucose, fructose, and isomaltose, etc.), synthetic (aspartame, saccharin, sucralose, acesulfame-K, cyclamate, alitam, and neotame, etc.)
5	Superdistintegrants	0-8 %	Sodium starch glycollate, crosspovidone, and polacrilin potassium
6	Flavouring agent	Q. S	Peppermint, cinnamon, clove, lemon, orange, vanilla, and chocolate,etc
7	Surfactants	Q. S	Sodium lauryl sulfate, benzalkonium chloride, Tween, , polysorbate, and poloxamer 407,
8	Colouring agents	Q. S	Titanium oxide, silicon dioxide, and zinc dioxide,

Formulation Techniques for Preparation of Oral Thin Film:

Conventional Approaches:

1. Solvent casting method.
2. Hot-melt extrusion.

3. Semisolid casting.
4. Solid dispersion extrusion.
5. Rolling.

Solvent Casting Method: The water-soluble polymers are first dissolved in water at 1,000 rpm while being heated to 60°C in this process. The remaining excipients- colors, flavourings, sweeteners, etc. are all dissolved separately. The resulting solutions are then fully combined while being stirred at 1,000 rpm. The API that has been dissolved in a suitable solvent is added to the resulting solution. A vacuum is used to extract the trapped air. The finished mixture is poured into a film and allowed to dry before being cut into the required number of pieces.

Hot-melt Extrusion: The initial mass is created using carriers in the hot melt extrusion process. The medication is combined with carriers to create initial mass, which is then dried after obtaining a solid mass. The extruder is then fed with dry, granular material. In order to process the granules inside the extruder barrel for around 3–4 minutes so that mass is adequately melted, the extruder screw speed should be set at 15 rpm. The resultant extrudate is then compressed into a cylindrical calendar to produce a film [28-30].

Semi-solid Casting: When using acid insoluble polymer as a film constituent, this approach is often recommended. In this initial step, water is used to dissolve the water-soluble polymers. The resulting solution is incorporated into the separately created acid-insoluble polymer solution. The two solutions have been suitably blended. After combining the two solutions, the resultant final solution is given a proper dosage of plasticizer to create gel mass. Finally, using heat-controlled drums, the gel mass is cast onto the films or ribbons. The ideal film thickness is between 0.015 and 0.05. The ratio of film-forming polymer to acid-insoluble polymer should be 1:4.

Solid Dispersion Extrusion: To enable loading of the medication, the method incorporates solid drug dispersion integrated in melted polymer solution. To create a solid dispersion, the medication is dissolved in a suitable liquid solvent and the resulting solution is added to a melt of a suitable polymer that may be generated at temperatures below 70°C. Finally, using dyes, they produced solid dispersions that were then formed into films.

Rolling Method: In the rolling process, the film-forming polymer solution and the drug solution are fully combined before the resulting solution or suspension is sent through a roller. Specific rheological considerations should be made for the solution or suspension. The film is cut into the necessary shapes and sizes after being cured on rollers [29-33].

Evaluation Parameters:

Organoleptic Test: Color, flavour, and taste are the required organoleptic attributes for a fast-dissolving formulation. The formulation should have appropriate organoleptic pleasant properties since it will dissolve in the mouth. He helps patients accept a formulation, and when oral films are given to youngsters, they should have appealing colour. Therefore, the colour of the formulation should be consistent and appealing. Visual examination can be used to assess colour. The smell is another organoleptic characteristic. The flavour added to the recipe should give it a pleasing aroma. By using a flavouring ingredient, the smell of the polymer, medication, and any other excipient should be concealed.

Taste is another crucial element that has to be considered. Special human taste panels are utilised to assess the flavour. The ability to differentiate between different sweetness levels in taste-masking formulations has also been demonstrated in experiments utilising electronic tongue measurements.

Surface pH Test: Evaluation of the surface pH of the film is required because the rapid dissolving strip's surface pH might have negative effects on the oral mucosa. The pH of the film's surface should be 7 or nearly neutral. A mixed pH electrode can be used for this.

OTF was made slightly damp with water, and the pH was determined by placing an electrode across the surface of the oral film. At least six films of each formulation should be used in this investigation so that the mean and standard deviation (SD) can be determined [34-35].

Thickness: Micrometer screw gauges or calibrated digital Vernier Calipers are used to measure film thickness. The recommended range for film thickness is 5-200 m. It is crucial to determine uniformity in the thickness of the film since this is directly connected to the accuracy of the dose distribution in the film. The thickness should be assessed at five distinct points (four corners and one in the centre).

Dryness/Tack Test: There are a total of eight drying phases for films, including set-to-touch, dust-free, tack-free (surface dry), dry-to-touch, dry-hard, dry-through (dry to handle), dry-to-recoat, and dry print-free. Tack describes how firmly a strip sticks to an accessory (such as a sheet of paper) after being rubbed against it. There are other instruments available for this research.

Tensile Strength: The highest stress that may be applied to a strip specimen before it breaks is its tensile strength. As shown in the equation below, it is computed by dividing the applied load at rupture by the cross-sectional area of the strip:

Tensile strength = Load at failure × 100/Strip thickness × Strip width

Percent Elongation: Strain is the stretching that occurs when tension is applied to a film (2×2 cm^2) sample. In essence, strain is the distortion of a strip prior to its failure under stress. The Hounsfield universal testing machine is used to measure it. In general, strip elongation rises as plasticizer content does. It is determined using the formula [37]:

% Elongation = Increase in length of strip × 100/Initial length of strip

Tear Resistance: A film's ability to resist being torn when a weight or force is applied to the film specimen is referred to as tear resistance. The main applied load is 51 mm/min, which is quite low. Newton or pounds of force are used to measure tear resistance. In other terms, it is the amount of force needed to completely destroy the specimen.

Young's Modulus: Young's modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

Young's modulus = Slope × 100/Strip thickness × Cross head speed

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation.

Folding Endurance: Film is become brittle by folding endurance. The procedure used to calculate endurance value is repeatedly folding the film specimens (2×2^2) at the same location until they break, or a noticeable fracture is noticed. The computed folding endurance value is the number of folds the film can endure without cracking or breaking [38].

Transparency: A straightforward ultraviolet (UV) spectrophotometer may be used to assess the transparency of oral film. The spectrophotometer cell's interior side is where the film specimen is put. Film transparency is determined using the following formula:

Transparency = (log T600)/b = −€c

Where T600 is the transmittance at 600 nm and b is the film thickness (mm) and c is concentration.

Scanning Electron Microscopy: Electron microscopy may be utilised to examine the surface morphology of the film between various excipients and drug scans. At a magnification of 1000, the film sample should be set up in a sample holder. Using tungsten filament as an electron source, different photomicrographs can be obtained.

***In-vitro* Disintegration Test:** When an oral film comes in touch with saliva or water, it begins to disintegrate at that point. The time of disintegration should be in the range of 5 to 30 seconds for a film that dissolves quickly. Disintegration time can be investigated using a USP (United States Pharmacopoeia) disintegration device. Another approach involves dipping the film in 25 ml of water in a beaker to visually assess the disintegration time. Gently shaking the beaker is required, and the moment the film begins to dissolve or degrade should be noticed.

***In-vitro* Dissolution Studies:** Under typical circumstances of the liquid/solid interface, temperature, and solvent concentration, dissolution is the quantity of drug ingredient that enters the solution per unit time. For dissolving testing, you can use the typical basket or paddle equipment

mentioned in any of the pharmacopoeias. The sink conditions and greatest dosage of API will largely determine the choice of dissolving media. Dissolution medium temperature should be kept at 37 0.5°C, and rpm should be kept at 50. The use of the paddle device has the drawback because oral films have a propensity to float above the dissolution media [39].

Drug Content Uniformity: Any standard assay technique specified for the specific API in any of the standard pharmacopoeia can be used to ascertain this. By measuring the API content in each individual strip, content consistency is assessed. 85 to 115% is the maximum content homogeneity.

Permeation Studies: Even though the oral mucosa has a permeability that is 4 1000 times larger than the skin's, permeation tests need to be done. Modified Franz diffusion cells and porcine buccal mucosa can be utilised to examine the permeability. There are donor and receptor compartments in a Franz diffusion cell. Mucosa is positioned between the two compartments, and it should have the same size as the head of the receptor compartment. The receptor compartment is filled with buffer and kept at 37 0.2°C while being stirred by magnetic beads at a speed of 50 rpm to maintain thermodynamics. Keep a film specimen in close contact with the mucosal surface after moistening it with a few drops of simulated saliva. One millilitre of simulated saliva with a pH of 6.8 should be placed in the donor compartment. At certain intervals, samples are removed and are replaced with an equal volume of new media. An appropriate analytical technique can be used to calculate the percentage of drug permeation [38].

Percentage Moisture Loss: Films with a surface area of 2 x 2 cm2 are carefully cut and weighed on an electronic balance to calculate the % moisture loss. The films were weighed and then stored in desiccators with fused anhydrous calcium chloride. The desiccator should be used to store the films for 72 hours. They are removed after 72 hours, weighed once more, and the formula is used to calculate the % moisture loss of the films:

Percent moisture loss = (Initial weight - Final weight)/Initial weight × 100

The percentage moisture loss studies are done to determine physical stability and integrity of the film.

Determination of % Yield of Buccal Patches: Percentage yield of buccal patches can be calculated by the following formula [39]:

% yield = Mass of the buccal patches obtained/Total weight of drug and polymer × 100

Stability Study: According to the International Conference on Harmonization's (ICH) recommendations, stability studies should be conducted. The produced formula was packaged in a unique manner. It was first wrapped in a butter paper, which was followed by an aluminium foil wrap.

The packaging was then put into an aluminium bag and heat sealed. Formulations should be stored between 30°C and 40°C with a relative humidity (RH) between 60% and 75%, respectively. The films were assessed for drug content, disintegration time, and physical appearance after three months [40].

Packaging and Storage: The fast-dissolving dosage forms must be protected throughout production and storage using expensive packaging, specialised processing, and particular care. Single packing must be used. The most popular type of packaging is an aluminium bag. The Rapid card, a unique and patented packaging solution created by APR-Labtec, is specifically made for the Rapid films.

Three films may be stored on each side of the Rapid card, which is the same size as a credit card. Each dosage may be removed separately [41-44].

Market Formulated Product of OTF:

TABLE 4: LIST OF MARKETED PRODUCTS [45-50]

Sr. no.	Brand Name	Type of Formulation	Application
1.	Zolmitriptan Rapidfilm	Zolmitriptan ODF	Migraine
2.	Setofilm	Ondansetron ODF	Nausea

3.	KP106	D-amphetamine ODF	ADHD
4.	Onsolis	Fentanyl buccal soluble films	Breakthrough pain (cancer)
5.	Rapidfilm	Ondansetron and Donepizil ODF	Nausea and psychosis
6.	Triaminic Thin Strips	Phenylephrine and diphenhydramine ODF	Cough and Cold
7.	Suboxone	Buprenorphine and naloxone (sublingual films)	Opoid dependence
8.	Gas-X Thin Strips	Simethicone (sublingual films)	Bloating and gas
9.	Sudafed PE dissolved strips	Phenylephrine ODF	Cough and Cold

Applications of OTF in Drug Delivery Systems: For treatments requiring quick drug absorption, such as those used to treat pain, allergies, sleep disorders, and diseases of the central nervous system, oral mucosal administration via sublingual, buccal, and mucosal channels with the use of oral thin film may become the preferred delivery technique.

Topical Applications: In order to distribute active chemicals, such as analgesics or antibiotics, in the context of wound care and other applications, the use of dissolvable films may be practical [50-51].

Gastro Retentive Delivery System: Dissolvable films are being studied as a dosage form for molecules of diverse molecular weights that are both weakly and completely soluble in water. The gastrointestinal tract's (GIT) pH or enzyme secretion may cause a film to dissolve, which may be employed to treat gastrointestinal disorders [52].

Diagnostic Devices: Dissolvable films can be filled with sensitive reagents to permit controlled release when exposed to biological fluids or to make isolation barriers for separating numerous reagents to enable a timed response inside a diagnostic device [53-54].

CONCLUSION: As opposed to tablets, several pharmaceutical companies are now producing oral thin films that dissolve quickly. Films combine the benefits of liquid dosage forms with those of tablets, such as exact dose and simple administration (easy swallowing, rapid bioavailability). OTFs are new, innovative drug delivery methods that are crucial in emergency circumstances when quick action is necessary. They fill a demand by enabling children, the elderly, and the general public to discreetly take their prescriptions whenever and wherever they are needed. This technology offers a solid foundation for the creation of patent-compliant items and for extending the patent protection of currently available products. Fast-dissolving oral thin films can be used for a variety of purposes, including sublingual and gastro-retentive delivery systems in addition to buccal fast-dissolving systems. Future uses might involve employing laminated multilayer films to combine incompatible active medicinal components into a single product. The incompatible active medicinal components may be separated by an inactive film layer. Thin films can include active medicinal components with high transmucosal flux rates for gradual dissolution into buccal or sublingual areas. It is also possible to integrate medications coated with controlled release polymers. This technology is being studied extensively and there is wide scope for further research in this field.

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FROM CONCEPT TO REALITY: THE RISE OF MESSENGER RIBONUCLEIC ACID IN MEDICAL MARVELS

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Keywords:

mRNA technology, mRNA vaccines, Genetic disorders, Targeted drug delivery

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ABSTRACT: Recent years have witnessed remarkable advancements in biomedical sciences, particularly in the realm of mRNA (messenger ribonucleic acid) technology. This manuscript offers a detailed overview of the burgeoning field of mRNA and its profound implications in science and medicine. Beginning with an introduction that elucidates the fundamental concepts and historical evolution of mRNA technology, the discussion progresses to an in-depth exploration of its structure, function, and pivotal role in modern medicine. The differences between mRNA and DNA are clarified to underscore the unique attributes of mRNA. A significant focus is given to mRNA vaccines, hailed as breakthroughs in preventive medicine. The exploration extends to mRNA therapeutics, highlighting their potential in targeted drug delivery and their ability to overcome traditional pharmaceutical challenges. Issues surrounding the efficacy and safety of mRNA applications are addressed, emphasizing importance of safety and ethical considerations. Present difficulties and potential paths in mRNA technology are discussed, underscoring ongoing research and innovative prospects. This review elucidates the transformative potential of mRNA technology, offering insights into its current applications, challenges, and promising future perspectives. As mRNA continues to revolutionize medicine, understanding its intricacies is vital for navigating the forefront of biomedical innovation.

INTRODUCTION:

Current Trends in mRNA Research: The "blueprint" of human cells is found in messenger RNA, a naturally occurring molecule (mRNA). It can create immunogens that target proteins for therapeutic purposes and trigger immune responses *in-vivo* to fight a range of pathogens [1].

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The development of vaccines intended to treat as well as prevent disease has recently placed a significant emphasis on based on RNA technologies. As a result of this, mRNA vaccines have developed greatly in recent years and are now an invaluable tool for treating and preventing infections, especially in the case of SARS-CoV-2 infection.

By using targets present in viral genome, mRNA vaccines can be developed and produced more quickly than other common vaccines. Dendritic cells have the ability to deliver mRNA vaccines *ex-vivo*. Polymers, peptides, lipid nanoparticles, free

mRNA in solution, and delivery carriers can also be used to encapsulate them. Because mRNA technology can prevent cancer and infectious diseases, it has shown a great deal of promise in clinical applications [2]. There has been a lot of interest in mRNA technology due to its amazing therapeutic potential. The wide application of mRNA molecules depends on the development of stabilization methods. Although mRNA delivery has been reviewed extensively, relatively little of it has addressed the root causes of mRNA instability and strategies for mitigating its problems. Every living cell must contain mRNA, which acts as a mediator in the genetic information transfer process. Research interest in mRNA therapeutics has increased significantly due to mRNA's inherent versatility [3].

Factors like toxicity, vector size, and unwanted immune responses limit its ability to spread. An important advancement in mRNA delivery has been the rising interest in different non-viral nanovehicles, including lipid-based nanoparticles, polymeric nanoparticles, lipid-polymer hybrid nanoparticles, and more [1]. It is essential to remember that the transient effects of mRNA are short-lived and easily controlled, which lowers the likelihood of unforeseen consequences and long-term toxicity [4]. Because of its effectiveness, low cost, quick development, and safety, scientists believe mRNA vaccine technology will soon become the norm in the field [5]. Since, lipid nanoparticle-based messenger RNA (mRNA) vaccines showed remarkable clinical results in the COVID-19 pandemic, mRNA has gained recognition as a potent therapeutic agent for a variety of human diseases, especially cancerous tumors. mRNAs are used in immunomodulatory proteins, cancer vaccines, therapeutic antibodies, and adoptive T-cell therapies, among other applications, in the fight against cancer [6]. The three areas of mRNA vaccine technology that have seen the most significant advancements recently are: 1) mRNA sequence engineering; 2) the creation of techniques that facilitate the easy, quick, and large-scale cGMP production of mRNA; and 3) the creation of extremely effective and secure mRNA vaccine delivery materials [7].

Key Milestones: First identified in the early 1960s, messenger RNA (mRNA) was introduced enter cells to express proteins in 1970s [8]. They found that RNA taken from tumour cells carrying the Mengo encephalitis virus could be used to create infectious viral particles. Malone and associates proposed drug application of mRNA in 1989. Then, Zhou and associates demonstrated in 1994 that mRNA could be utilized to create vaccines. Ying and colleagues proposed the use of mRNA as a cancer-fighting tool in 1999. An mRNA vaccine may stimulate the body's defenses against prostate cancer, according to a 2003 trial. The first mRNA-based cancer vaccine, AVX701, started clinical trials in 2007. New strategies for enhancing mRNA vaccines were created in 2019. RNA vaccines were also delivered *via* lipid nanoparticles.

A study on a COVID-19 mRNA vaccine in 2021 produced encouraging findings. Research on mRNA vaccines for cancer and the flu is currently underway, demonstrating their potential as an effective preventive and therapeutic measure [9]. The concept of using mRNA to encode proteins for immunisation or protein replacement was first validated *in-vivo* in 1990 by Wolff *et al.*, who demonstrated that mice could produce a target protein after intramuscular injection. But decades passed before the promise of this technology could be clinically validated. Technical problems with mRNA stability and delivery as well as a brief shift in industry focus, funding, and research priorities towards DNA vaccines in the 2000s contributed to this delay4. Meanwhile, some dedicated researchers continued to work on mRNA, a single-stranded nucleic acid, because of its potential advantages as a vaccine component [10].

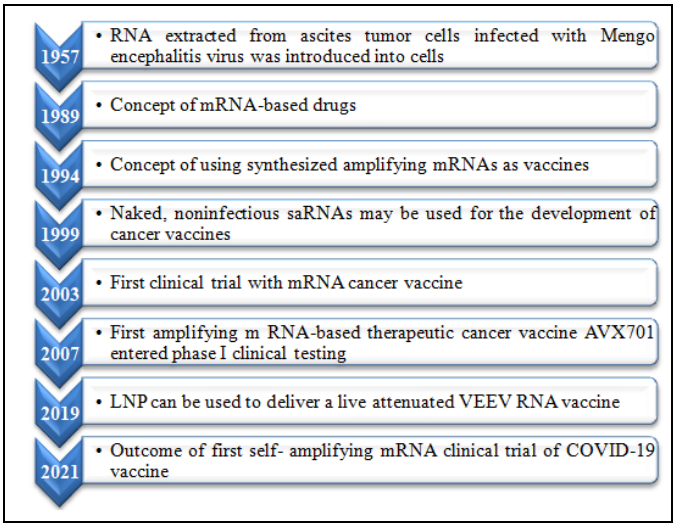

FIG. 1: KEY MILESTONES

Basics of Vaccination: Vaccination is the most effective means of controlling and preventing illness; it has saved many lives from cancer and infectious diseases [2].

Each year, vaccinations save countless lives and prevent millions of illnesses. Because of the widespread use of vaccines, the smallpox virus has been eradicated and the prevalence of measles, polio, and other childhood diseases has drastically decreased globally. Conventional vaccination strategies offer long-lasting protection against a range of serious illnesses. These strategies include live, attenuated, and inactivated pathogens as well as subunit vaccines [11].

One of the best public health tactics we have in the fight against infectious diseases is vaccination. Since then, vaccines that prevent 30 deadly illnesses have replaced the live cowpox virus that vaccination pioneer Edward Jenner used in 1798 to prevent smallpox. These vaccines save 6 million lives annually, extend life expectancy, and improve health for people of all ages by providing immune protection against multiple pathogen types.

Additionally, utilization of immunization in prevention and treatment of cancer is growing. Additionally, it can lessen the need for antibiotics to treat bacterial infections, thereby reducing the likelihood that antibiotic resistance will arise. However, licensed vaccinations against several serious, chronic, and life-threatening infectious diseases are still not available [6]. Nucleic acid therapeutics appear to be promising alternatives to conventional vaccination strategies [11].

The review explores the groundbreaking advancements in mRNA (messenger ribonucleic acid) technology and its profound impact on modern medicine. The purpose of the review is to provide insight into the revolutionary potential of mRNA in transforming disease prevention and treatment. As a recent and rapidly evolving topic, mRNA technology shows its promising applications in combating infectious diseases, genetic disorders, and cancer.

Understanding MRNA: A Simple Overview: The poly (A) tail, a stop signal-containing coding sequence, 3' untranslated region (3' UTR), 5' untranslated region (5' UTR), also referred to as leader RNA, and a 5' cap make up mRNA. Each mRNA template yields multiple copies of the corresponding protein when translated by ribosomes and tRNA in the cytoplasm, providing a quantitative advantage over individual protein production [12].

The 5' UTR is where protein translation starts, and ribosome binding depends on the preinitiation complex's formation. As per the RNA translation scanning model, the 5' UTR's secondary structures and sequence have an impact on both translation efficiency and mRNA stability. Additionally, some viruses, such as the encephalomyocarditis virus, can induce cap-independent expression of proteins because a 5' UTR internal ribosome entry site (IRES). IRES primarily responsible for translating the 5' UTR's downstream open reading frame (ORF) sequence.

For better translation efficiency, the Kozak sequence is typically placed next to the 5' UTR. The elements of the 3' UTR affect the stability of mRNA. Eukaryotic mRNAs typically have mRNA degradation signals in their 3' UTR, which have an impact on the mRNAs' stability. Iron-responsive elements (IREs), a separate but equally important segment of the 3' UTR, regulate the translation and stability of mRNA [13].

mRNA vs. DNA: Basic Differences: More benefits than DNA therapy are associated with mRNA therapy. While mRNA delivery can achieve strong transfection efficiency using non-viral vectors including lipids and polymers, viral vectors are necessary to produce high transfection effectiveness in DNA therapies. Additionally, using *in-vitro* transcription in cell-free environment guarantees production of mRNA vaccines. On the contrary, viruses or particles that resemble viruses, mRNA does not elicit immune responses specific to vectors or carriers (VLPs). Furthermore, since mRNA functions directly in the cytoplasm and transcription requires DNA entry into the nucleus to occur before protein synthesis, antigens in mRNA vaccines are generated more quickly. In cells, mRNA experiences molecular alterations like deadenylation and decappingbefore being hydrolyzed by RNase. These changes ensure the transient expression of exogenous mRNA treatments, enhancing safety [12, 13].

TABLE 1: mRNA VS. DNA

Aspect	mRNA	DNA
Delivery Vectors	Non-viral vectors (e.g., lipids, polymers)	Viral vectors required for high transfection efficiency
Safety	Generated via *in-vitro* transcription in a setting devoid of cells.	Can pose safety concerns due to possibility of potential integration into host genome with viral vectors
Immunogenicity	Does not elicit vector- or carrier-specific immunogenicity	May induce immune reactions due to viral vector components
Cellular Location	Functions in the cytoplasm	Enters the nucleus and undergoes transcription
Protein Expression Speed	mRNA vaccines contain antigens that can be expressed more quickly	Protein expression may be slower due to nuclear transcription
Location of Action	Present in the cytoplasm; no nuclear entry is required	Must enter the nucleus for transcription
Stability	Less stable compared to DNA	More stable compared to mRNA
Amplification	Transcription to protein; requires translation	This causes several mRNA molecules to be produced
Duration of Protein Expression	Transient nature; relatively short-term protein production	Longer persistence; potential for long-lasting expression
Speed of Development	Rapid construct generation based on genetic sequence	Fast technology for vaccine production in epidemics
Immune Response Amplification	Effective in eliciting immune response against small amounts of protein	Efficient in amplifying immune response against the expressed protein
Manufacturing Advantages	Fast and generic procedures as opposed to recombinant proteins or conventional vaccinations	Offers rapid vaccine production in response to emerging diseases

mRNA Vaccines: A Breakthrough in Preventive Medicine:

How do mRNA Vaccines Work: For an mRNA vaccine to work, the target cells must be successfully injected with it. Once it enters cytoplasm, translated into the appropriate proteins. mRNA cannot enter the cytoplasm without first passing through negatively charged phospholipid bilayer of cell membrane. Molecules that can enter cells through passive diffusion are usually limited to molecular weights of less than 1000 Da. Thus, a carrier is needed to aid mRNA passage into cytoplasm of the cell. Presently, LNPs administer mRNA vaccines the most frequently; these vaccinations have four difficult components and inflammatory side effects.

It makes sense to conduct a thorough investigation into novel delivery strategies. Between translating DNA-encoded proteins and having cytoplasmic ribosomes synthesize proteins, mRNA is in an intermediate stage of the protein synthesis process. The two main forms of RNA that are being studied as potential vaccines are self-amplifying virally generated RNA and non-replicating mRNA. Self-amplifying RNAs enable high levels of protein synthesis and RNA amplification inside cells because they carry the genetic information necessary for both antigen and the viral replication machinery. In addition to target antigen, traditional mRNA-based vaccinations also have 5' and 3' untranslated regions (UTRs) [9]. The anatomical and physiological traits of immunization sites, like muscles, lymphatic organs, and epidermis, affect vaccine effectiveness, making the delivery route of mRNA vaccines essential. For optimal effects, vaccinations can be administered either locally or systemically [1]. A virus-specific T-cell response was successfully elicited in mice injected with liposome-coated mRNA encoding an influenza nucleoprotein in the 1990s, highlighting potential of mRNA therapeutics as novel vaccination approach [14].

Innovations in Delivery Systems: Viral and non-viral vector delivery methods are the two primary categories for mRNA vaccines. Enhancing delivery techniques to target particular tissues or cells increases efficacy and safety. Key non-viral vectors are cationic liposomes (LNPs), which were identified in the 1960s. FDA-approved lipid and LNP medications, like ion is able cationic lipids (iLNPs), use proteases, polymers, LNPs, and cell-based administration to efficiently deliver RNA vaccines into the cytosol. Both viral and non-viral tactics increase efficacy and shield mRNA from deterioration. On the other hand, immune responses and insertional mutagenesis are safety concerns associated with viral vectors. Major challenges are the instability and vulnerability of RNA.

Direct injection of naked mRNA was one of the early techniques; although simple to produce, it is less immunogenic and stable. Because of their stability, protection, and biocompatibility, LNPs have emerged as the go-to carriers. Electrostatic interactions between polymers and mRNA form polyplexes, which enhance mRNA's immunogenicity and cellular absorption while also protecting it. Target specificity, stability, safety, and transfection efficiency are all improved by the use of different encapsulation techniques in polymeric nanoparticles, which are derived from polymers like polylactic-co-glycolic acid and PEG. The choice of delivery mechanism depends on the mRNA vaccine type, desired attributes, and target audience [15].

Routes of Administration: The amount, speed, and efficacy of immune response are directly impacted by the distribution and formulation of mRNA vaccines. The ways in which LNP-mRNA is administered affect its distribution, rate of expression, and therapeutic outcomes. Intramuscular (IM), subcutaneous (SC), intradermal (ID), and intravenous (IV) are common routes of administration. IV injections enable high protein production, while IM is the predominant method due to efficient absorption by myocytes and larger injection volumes, reducing site reactions but increasing systemic absorption. SC injections also allow larger volumes, reducing pressure and discomfort. Each route has unique benefits and considerations for vaccine delivery and patient experience [13].

Success Stories: mRNA Vaccines in Action: Attempts to develop vaccines against parasites like Plasmodium and Schistosoma, and pathogens like HIV and Mycobacterium tuberculosis, have not yet produced effective immunity. Conventional vaccine platforms often fail to respond quickly, safely, effectively, and economically to epidemic outbreaks. The need for vaccines utilising in-host mRNA translation and in vitro mRNA transcription was brought to light by the COVID-19 pandemic. BioNTech and Pfizer's BNT162b2 trial represented a major advancement in public health. mRNA vaccines are safe, avoid integration hazards, and are highly effective in inducing strong humoral and T-cell responses. They share a quick, simple, and cell-free manufacturing process with DNA vaccines, making mRNA an ideal candidate for rapid therapeutic or preventive vaccines in new pandemics [16].

MRNA Vaccine Applications: Treatment of a number of refractory conditions, such as infectious diseases, cancer, metabolic genetic disorders, and heart and brain disorders, may be possible with the utilization of mRNA-based therapeutics. In-depth research on mRNA vaccines has been conducted over the last 20 years, looking at both their potential for treating and preventing cancer as well as their capacity to combat infectious diseases [13].

A stable and adaptable platform for cancer vaccines is offered by mRNA. A perfect mRNA vaccine would include several neoantigens, such as driver gene mutations and both predicted and confirmed mutations and be prepared in suitable nanoparticles and administered with suitable adjuvants. The most potent antigen-presenting cell, DCs, should be the target of a perfect mRNA vaccine. When it is successfully applied to clinical settings, our ability to fight cancer will be greatly enhanced [9]. The rapid development and utilizations of mRNA vaccines in the fight against the COVID-19 pandemic is one recent illustration of the significant impact that RNA therapeutics have had on medicine [14]. Pre-clinical and clinical studies are looking into using IVT mRNAs to replace missing or damaged proteins caused by genetic illnesses or in circumstances where protein delivery may be therapeutically beneficial. The potential of IVT mRNA to treat hepatic disorders, generate human stem cells, and regenerate cardiac tissues has been investigated [13].

Pharmacological Advancement of mRNA Vaccines: Messenger RNA vaccines offer many benefits over DNA plasmids, viral vectors, and traditional live-attenuated viruses. Unlike DNA, mRNA does not risk chromosomal integration, enhancing safety. Its short half-life and rapid degradation in host cells further improve safety and effectiveness. RNA vaccines can rapidly introduce mutations for tailored therapies or pandemic responses, showing high adaptability. Unlike live-attenuated and vaccinations using viral vectors, mRNA vaccines are not contagious and do not incorporate into host genome. Additionally, producing mRNA *in-vitro* is quick and cost-

efficient, underscoring the practical benefits of mRNA-based vaccinations [17].

mRNA in Therapeutics: mRNA therapeutics control pathogenic processes and provide therapeutic effects by using RNA molecules to translate particular proteins inside target cells. Protein replacement therapy holds promise for treating a range of illnesses, including cancer, heart disease, neurological disorders, and metabolic diseases. It replaces faulty proteins in diseases resulting in protein deficiencies. mRNA therapies that increase the production of Cas protein for gene editing are advantageous for gene editing techniques like the CRISPR/Cas system. Because mRNA therapies allow for the temporary production of transcription factors without the risk of mutagenesis, they are also used in stem cell engineering and the treatment of CAR T cells. Clinical trials are presently being conducted on several mRNA therapies [18].

Current Applications:

Beyond Vaccines: To fight infectious diseases, mRNA vaccines could be developed with potential uses in both therapy and prevention. mRNA vaccines containing the antigen of a pathogenic microorganism elicit robust and notable humoral and T-cell immune responses [13]. mRNA vaccines have surfaced as a novel approach to address this problem and have the potential to effectively combat infectious diseases [1].

SARS-CoV-2: The COVID-19 pandemic has caused severe harm to the world, with over 772 million cases of infection and over 6.9 million deaths by November 22, 2023. The FDA approved mRNA-1273 from Moderna and BNT162b2 from Pfizer-BioNTech in 2020 as vaccine candidates that have shown promise in combating the virus. BNT162b21 is composed of the ionizable lipid ALC-0315 and nucleoside-modified mRNA. An infectious virus known as single-stranded RNA (ssRNA) is the cause of SARS-CoV-2. Since the disease was first discovered in Wuhan, China in December 2019, it has shown signs of spreading throughout the world. The pharmaceutical sector has created several vaccines against the virus using various vector technologies [19]. Numerous illnesses, fatalities, and significant societal disruptions were brought on by COVID-19 pandemic. Main goals for public health were to develop "safe and effective" vaccines [16]. Rapid progress in mRNA vaccine development has been essential in controlling the coronavirus disease 2019 pandemic (COVID-19), indicating that such technology may be applied to other infectious disease outbreaks in the future. mRNA vaccines are particularly well-suited for vaccine development because of their adaptability, which allows antigens to be easily modified by changing the sequence within the mRNA coding region. This is especially true during crises of rapidly spreading infectious diseases [18]. Several vaccine technologies, including messenger RNA (mRNA) vaccine technology, were quickly developed in response to the 2019 COVID-19 outbreak to combat the pandemic and stop the disease's spread [5].

As it has prevented countless infections, hospitalizations, and deaths, the COVID-19 vaccination is most effective intervention in the fight against the global pandemic caused by SARS-CoV-2 infection. The application of current mRNA vaccine technology has enabled the development of vaccines that are highly immunogenic and efficient. Acute Respiratory Syndrome Severe The third new coronavirus that has caused serious illness in several nations over the past 20 years is SARS-CoV-2. COVID-19 has overtaken global healthcare systems, with over 250 million infections.

The most effective method of pandemic control to date has been the quick development and testing of highly effective vaccines made possible by the use of proven vaccine technology. In a broad vaccination campaign, authorized COVID-19 vaccines make use of a variety of platforms, including *in-vitro* transcribed messenger ribonucleic acid (mRNA) for the first time [20].

For those without underlying medical conditions, the majority of SARS-CoV2 infections do not represent a significant risk to life. In cases of severe infections, immune system may overreact in the lungs, resulting in the death of epithelial cells and alveoli, pulmonary edema, dangerously high vascular permeability, and even death. The spike protein present on the surface of SARS-CoV-2 binds to ACE2 receptors on host cells, enabling the virus to enter the cell [15].

Influenza Viruses: Influenza virus, a common respiratory pathogen that affects people worldwide, is a major threat to public health and world economy. mRNA-based vaccinations may prove to be an effective means of enhancing influenza immunity. mRNA-based influenza vaccinations have been demonstrated in numerous studies to elicit a strong and long-lasting immune response against the virus [1]. Because it is easy to test the effectiveness of mRNA vaccines against influenza virus in small animal models, possesses devices for evaluating T and B cell reactions., and has potential benefits, mRNA vaccines against influenza virus are among most studied. It may take at least six months to produce traditional, FDA-approved vaccinations against novel influenza pandemic viruses, during which time the public would not be protected [21].

Rabies Virus: Rabies, a fatal neurological illness affecting humans and other warm-blooded animals, remains a significant concern. CureVac has created CV7201, an mRNA vaccine for rabies, using cationic polypeptide protamine as delivery method. Preclinical studies involving mice and pigs have demonstrated that CV7201 effectively induces humoral immune responses and T-cell responses [1]. Recently, results from a study using a protamine-formulated, sequence-optimized conventional mRNA vaccine that encodes the glycoprotein of the rabies virus were published for the first time in humans (RABV-G). Strong neutralising antibody responses in pigs and protective immunity against a fatal intracerebral virus challenge in mice had previously been shown to result from this vaccination [22, 23].

mRNA Vaccines Targeting Zika Virus Infection: Pardi *et al.* independently reported the effectiveness of their nucleoside-modified conventional mRNA, formulated with LNP, against Zika infection. After two 10-mg i.m. or one 30-mg i.d. vaccination, respectively, both groups showed remarkable levels of neutralizing titers and protection against lethal challenge in mice, and after a single 50-mg i.d. vaccination in NHPs. To potentially increase the vaccine's safety, Richner *et al.* also tested an mRNA vaccine encoding a modified Zika prM-E antigen that contained mutations that destroyed the conserved fusion-loop epitope in domain II of the E protein [24, 25, 26].

HIV Virus: HIV poses a global health challenge, compromising immunity by targeting immune cells and increasing susceptibility to diseases and infections. According to estimates from Global Statistics, approximately 39.0 million individuals worldwide will be living with HIV by the end of 2022. Despite extensive research efforts, effective treatment for HIV remains elusive, highlighting the urgent need for prevention measures. Moderna has created an experimental mRNA HIV vaccine using the same platform technology as their effective COVID-19 mRNA vaccine. The vaccine has shown positive results in mice and non-human primates, proving its safety and effectiveness in producing a strong immune response against HIV. Moreover, the vaccination has been demonstrated to stimulate the generation of neutralizing antibodies [1].

mRNA Immunisations Against Parasitic and Bacterial Diseases: Recently, the efficacy of self-amplifying mRNA against parasitic diseases has been evaluated with malaria as the target disease. plasmodium macrophage migration inhibitory factor (PMIF), which suppresses memory T cells and allows the parasites to evade the immune system, is encoded by a self-amplifying mRNA vaccine. Self-amplifying mRNA vaccination stimulated humoral and cellular immune responses against PMIF, and anti-PMIF immunoglobulin G (IgG) blocked PMIF's pro-inflammatory effects. Tfh cell and GC response were enhanced, blood-stage latency after sporozoite infection was delayed, and memory CD4+ T cells with antigen experience and liver-resident CD8+ T cells were better differentiated. In addition, mice that had recovered from their infection but had been exposed to sporozoites once more were completely immune to contracting the infection again. Adoptive transfer of CD8+ or CD4+ T cells recapitulated protection against reinfection. This study showed how effective self-amplifying mRNA vaccination is at preventing the parasite's immune-evasion strategy[27, 28].

mRNA in Cancer Treatment: The emergence of mRNA-based cancer immunotherapy as a promising cancer treatment approach is due to the combination of mRNA and nanoparticle technology. Clinical trials have shown that mRNA-based cancer immunotherapy is safe and effective, leading to significant tumor remission in certain

patients. Because of its adaptability, mRNA can be successfully employed in a variety of cancer immunotherapy methods [4]. Because they have therapeutic as well as preventive benefits, cancer vaccinations can be a good substitute for cancer immunotherapy.

Tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs), which can be used to produce long-lasting therapeutic effects by attacking and killing cancer cells that over-express these antigens, are the specific targets of vaccines that stimulate immune memory. As a result, it is expected that mRNA vaccines will be an effective cancer treatment modality [1]. Immune checkpoint inhibitors are expected to be the future of mRNA cancer immunotherapy in conjunction with mRNA-based personalized therapeutic modalities such as tailored vaccines [4].

mRNA in Genetic disorders: Hereditary diseases like hemophilia, cystic fibrosis, and muscular dystrophy can benefit from the replacement or enhancement of deficient proteins or genes through messenger RNA therapy. Gene abnormalities affecting clotting factors are the cause of hemophilia, a bleeding disorder. Mutations in any gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR) cause cystic fibrosis, also referred to as lung disease. Mutations in the gene that produces the protein dystrophin result in muscular dystrophy. By introducing mRNA that encodes specific proteins or genes to those targeted regions, mRNA treatment can improve the function of diseased cells or tissues and reduce the symptoms of the underlying illness [20].

Genome Editing: Through genome editing, genetic diseases may be effectively treated by precisely adding, removing, or replacing DNA sequences at a specific locus in genomic DNA. Since, the groundbreaking discovery of the CRISPR/Cas9 system (clustered regularly interspaced short palindromic repeat-associated protein 9), gene editing has gained enormous popularity. Co-delivery of Cas9 mRNA and sgRNA can overcome the limitations of conventional CRISPR/Cas9 delivery by plasmid, minimise off-target effects, and achieve transient Cas9 protein expression [29].

Quality, safety, and efficacy of mRNA-Based Vaccines:

Safety of mRNA-Based Vaccines: A phase 1 dose-escalation, open-label trial with participants aged 18 to 70 or older examined the safety of mRNA vaccines using mRNA-1273. Two groups underwent the investigation: one comprised of individuals aged 18–55 who received a dose of 250 µg, and another group comprised older subjects who received either 25 µg or 100 µg. After the vaccination, a number of negative effects were noted, including the emergence of new chronic illnesses, unforeseen side effects, systemic and local side effects, and major side effects. Headaches, exhaustion, chills, muscle stiffness, and injection site soreness were a few of the frequent side effects. Antibody levels that neutralise viruses are linked to animal and human defence against SARS-CoV-2 and other viruses [30].

One benefit of mRNA manufacturing over most biologicals is that it doesn't require the use of cell cultures during production. Compared to more complex vaccine production methods, this trait's quick response time reduces the chance of contamination. RNA-based vaccinations against infectious diseases are evaluated for quality, safety, and efficacy by current regulations. Right now, the emphasis is on creating manufacturing procedures that can reliably yield products of superior quality. As a result, requirements need to be set for various crucial process steps, drug substances (DS), drug products (DP), intermediates, and acceptance criteria. Considerations include things like product yields and analytical technologies that enable accurate product characterization and quantification. These include things like product identity, purity, and quality. The quality of mRNA is assessed using gel electrophoresis and HPLC (high-performance liquid chromatography). Moreover, reverse transcription polymerase chain reaction (RT-PCR) or next-generation sequencing can be used to confirm the identity of the sample [29].

Efficacy of mRNA Vaccines: After the second vaccination dose, the efficacy of mRNA-1273 was evaluated primarily for its ability to prevent symptomatic COVID-19 infection, with the secondary goal being prevention of severe COVID-19 infection.

The vaccination showed 94.1% efficacy against symptomatic COVID-19, and no severe cases were reported among those who received the shot. The vaccination showed high efficacy against various COVID-19 variants in Qatar, including 88.1% against the alpha variant after the first dose and 100% after the second dose. It also showed 95.7% efficacy against severe COVID-19. Efficacy rates against the beta strain were 61.3% and 96.4% following first and second doses, respectively, demonstrating the vaccine's ability to successfully prevent infections, hospitalizations, and fatalities [30].

When compared to the majority of biological processes, mRNA manufacturing has the advantage of not requiring the use of cell cultures. The risk of contamination is lower than with other complex vaccine manufacturing processes because of its quick reaction time. Furthermore, the mRNA safety profile is favored by the transient expression and non-integrative nature of the cellular expression [31, 32]. Guidelines for regulations governing the assessment of RNA-based prophylactic vaccines for infectious diseases in terms of their efficacy, safety, and quality are currently under consideration. These days, focus is on developing manufacturing procedures that can produce goods of a high caliber and consistency [33].

Current Challenges and Future Perspectives:

Challenges in mRNA Technology: mRNA vaccines offer a promising substitute for conventional vaccines because of their quick growth, great potency, and inexpensive manufacturing. However, its physiochemical properties might affect organ distribution, cellular transport, and mRNA stability. High-quality mRNA is less likely to be degraded by RNAse during synthesis. The current generation of mRNA-based vaccines against SARS-CoV-2, when administered in combination, inhibit Th2-biased immune responses, a crucial step in preventing vaccine-associated enhanced respiratory disease. Viral infections are frequently associated with acute myocarditis; cases have been documented in otherwise healthy people following vaccination against smallpox or the flu. Despite the fact that lipid-based nanomaterials are used in several vaccines to transport mRNA, each vaccine requires a different storage temperature. The BioNTech/Pfizer BNT162b2 vaccine needs to be stored at –80^{o}C, while the Moderna mRNA-1273 vaccine has a six-month shelf life and needs to be kept at –20^{o}C. There are still many obstacles to overcome, even though mRNA vaccines are safer and can be made fast using easily obtained materials. Immunogenicity, instability, low transfection efficiency, inefficient targeted delivery, and bio-incompatibility are still problems. The physical characteristics of messenger RNA (mRNA) present various obstacles to its conversion into specific antigens. These features include its high molecular weight, negative charge, susceptibility to RNases, and presence of both intracellular and extracellular barriers. Moreover, a large amount of mRNA is ambushed in endosomes at the time of entry, which prevents it from entering the cytoplasm and carrying out its intended functions. IVT mRNA transcripts have a brief half-life of five minutes in sera, indicating that they are unstable and readily broken down by primers [13].

Future Perspectives: The recent success in developing mRNA-based COVID-19 vaccinations has led to an explosion in preclinical and human studies exploring the potential of mRNA vaccines. Current preclinical and clinical research has demonstrated the effectiveness of mRNA technology in treating range of viral infections, like Ebola, Zika, Streptococcus, and Toxoplasma gondii. The development of mRNA vaccines against numerous cancer types has advanced. Recent developments in innate immune monitoring and *in-vivo* delivery technologies have sped up the development of mRNA vaccines, as demonstrated by the rapid development of mRNA-based COVID-19 vaccines. There are currently only two vaccines against cancer that are approved by the FDA, and they are for hepatitis B and human papilloma viruses [17].

CONCLUSION: Starting from its early discovery in the 1950s and 1960s and continuing for more than 50 years, the development of mRNA technology is a remarkable example of scientific innovation in action. During this journey, scientists have discovered the profound potential of messenger ribonucleic acid (mRNA), revealing avenues for ground-breaking discoveries that serve as cornerstones of contemporary medical innovation. The development of mRNA vaccines, which provide faster development and scalability

than those of traditional vaccine approaches, marks a turning point in preventive medicine. The efficacy and potential of mRNA vaccines to transform disease prevention globally are demonstrated by their success stories, especially in the fight against the COVID-19 pandemic. mRNA therapies have great potential to treat a wide range of illnesses, including cancer and genetic disorders, in addition to vaccinations. But as is the case with any new technology, safety and morality must always come first. Fostering public trust and confidence in these ground-breaking therapies requires ensuring the safety of mRNA applications through stringent testing and adherence to regulatory guidelines. It seems that mRNA technology has a bright future ahead of it, with continued research efforts poised to overcome present obstacles and unlock even greater therapeutic potential. We can use mRNA to address some of the most urgent medical issues facing humanity and usher in a new era of universal health and well-being by continuing to innovate and work across disciplines.

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NADIFLOXACIN AND ADAPALENE: A REVIEW ON REPORTED METHODS FOR PURPOSE OF VALIDATION AND QUALITY MONITORING

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ABSTRACT: *Acne vulgaris* is a common chronic inflammatory skin disease found predominantly in adolescents in both sexes. The best acne treatment inhibits bacterial growth, encourages the shedding to the skin cells to unclog pores. Treatment for acne includes topical agents and systemic agents. Its quality monitoring becomes essential for assuring quality products for human care. So, for that purpose a detailed study of review was done including reported and validated methods, official monograph methods for estimation of Nadifloxacin and Adapalene. It was found from a literature survey that among all reported evaluation methods the most widely and predominantly followed method is HPLC. Other methods reported were UV, HPTLC. A conclusion was made that there is lack of evaluation analytical methods for simultaneous estimation of Nadifloxacin and Adapalene in combined dosage form.

INTRODUCTION: Acne vulgaris is common chronic inflammatory skin disease found predominantly in adolescents in both sexes. The lesion is formed which are more commonly seen on the face, on upper chest and upper back. The appearance of lesions near puberty is due to physiological hormonal variation. Mild acne is defined as presence of clogged skin follicles which is also known as comedones on to the face with inflammatory lesions. People with mild acne don't get large areas of red, inflamed skin or acne scarring.

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Moderate acne occurs when a high number of inflammatory papules and pustules occur on the face when compared to mild cases of acne. They are also found on the trunk of the body. Severe acne occurs when nodules (which is also called as painful bumps) are the characteristic facial lesions and the involvement of trunk is more. Sign and symptoms of acne varies depending upon severity of condition: White heads, Black heads, Small red tender bumps, Pimples, painful lumps (nodules).

Androgen stimulates secretion of the sebaceous gland causing them to enlarge and secrete the natural oil, sebum which rises up to top of the hair follicle and flows out on to the skin surface. In adults who develop acne, androgenic stimulation produces a high response in the sebaceous gland so, the formation of acne occurs when accumulated sebum plugs the pilosebaceous ducts.

This accumulated material leads to the formation of comedones. Treatment: The best acne treatment inhibits bacterial growth, encourages the shedding to the skin cells to unclog pores. Treatment for acne includes topical agents and systemic agents. Topical agents used in treatment of acne vulgaris: Treatment of acne vulgaris involves retinoids and antimicrobial and some antibacterial drug use. Topical retinoid acts to normalise the maturation of follicular epithelium and reduces inflammation and enhances the penetration of topical medication.

Nadifloxacin is a topical antibiotic that treats bacterial skin infections and acne. It's a second-generation fluoroquinolone that's effective against aerobic and anaerobic bacteria, including Gram-negative bacteria, Gram-positive bacteria, Propionibacterium species, Streptococcus species, and Staphylococcus species. Nadifloxacin works by preventing the synthesis of essential proteins and inhibiting the activity of bacterial enzymes. Nadifloxacin is intended for external use only. Some side effects that may occur during treatment include burning and itching, contact dermatitis, dryness, and skin irritation [1].

Adapalene is a third generation topical retinoid primarily used in the treatment of mild-moderate acne, and is also used off-label to treat keratosis pilaris as well as other skin conditions. Studies have found adapalene is as effective as other retinoids, while causing less irritation. It also has several advantages over other retinoids [2]. The adapalene molecule is more stable compared to tretinoin and tazarotene, which leads to less concern for photodegradation.

Nadifloxacin [3, 4]:

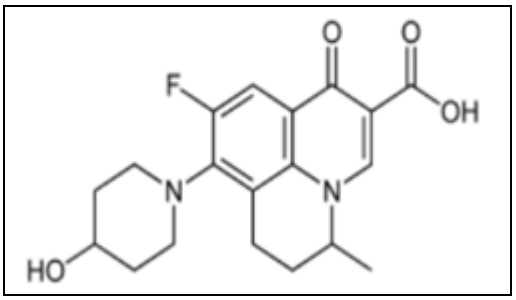

FIG. 1: STRUCTURE OF NADIFLOXACIN

It is also chemically more stable compared to the other two retinoids, allowing it to be used in combination with benzoyl peroxide. Due to its effects on keratinocyte proliferation and differentiation, adapalene is superior to tretinoin for the treatment of comedonal acne and is often used as a first-line agent.

Chemical Name: 9-Fluoro – 8 - (4 – hydroxyl - 1-piperidinyl) – 5 – methyl – 1 – oxo - 6, 7-dihydro-1H, 5Hpyrido[3, 2,1-ij] quinoline-2-carboxylic acid

Molecular Formula: $C_{19}H_{21}FN_2O_4$

Molecular weight 360.379 g/mol

Drug Category: Antibacterial

Mechanism of action: Inhibits enzyme DNA gyrase that is involved in bacterial DNA synthesis and replication, thus inhibiting the bacterial multiplication.

Indication: Used in treatment of bacterial skin infection *i.e.* acne vulgaris

Adapalene [5, 6, 7]:

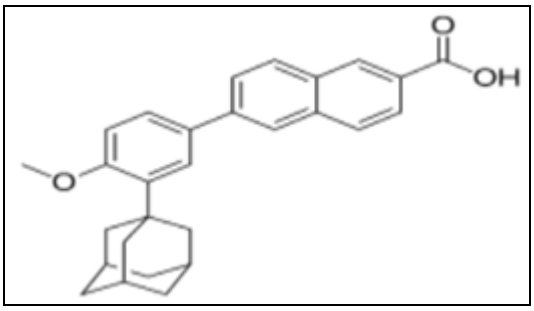

FIG. 2: STRUCTURE OF ADAPALENE

Chemical Name: 6 - [3 - (adamantan – 1 - yl) - 4-methoxyphenyl] naphthalene -2-carboxylic acid.

Molecular Formula: $C_{28}H_{28}O_3$

Molecular Weight: 412.52 g/mol

Drug Category: Topical retinoid

Mechanism of Action: It acts on retinoid receptor. It is modulator of cell differentiation, keratinization and inflammatory processes which is pathology of acne vulgaris. Indication Used in treatment of acne vulgaris.

Mechanism of Action (in Combination): Nadifloxacin is an antibiotic. It kills bacteria by preventing them from reproducing and repairing themselves.

Adapalene is a form of vitamin A which prevents accumulation of sebum (skin's natural oil), unblocks the pores and allows natural exfoliation of the outer layers of skin. Combination is approved by CDSCO on 17-7-2015. The gel is used in acne vulgaris. The dose is 10 mg of nadifloxacin and 1mg of adapalene.

FIG 3: COMBINATION MARKETED FORMULATION

Method for Analysis: Quality monitoring is essential to certify the quality, safety, and efficacy of pharmaceutical products. So, Analytical Methods are developed and validated as per ICH guideline to assure quality. The methods reported in the literature for evaluation of Nadifloxacin and Adapalene were UV-Visible spectroscopy, HPLC, HPTLC, UPLC. The summary of reported methods is shown in **Fig. 4** and **Fig. 5.**

Literature review shows that many methods has been developed for Nadifloxacin but with other drugs like Mometasone furoate, Terbinafine hydrochloride, Clobetasol Propionate and Miconazole nitrate and also for adapalene in combination with other drugs like Benzoyl peroxide, Clindamycin Phosphate. But no method has been reported for simultaneous estimation of Nadifloxacin and Adapalene. The summary of reported methods is depicted in below **Table 1** and **Table 2.**

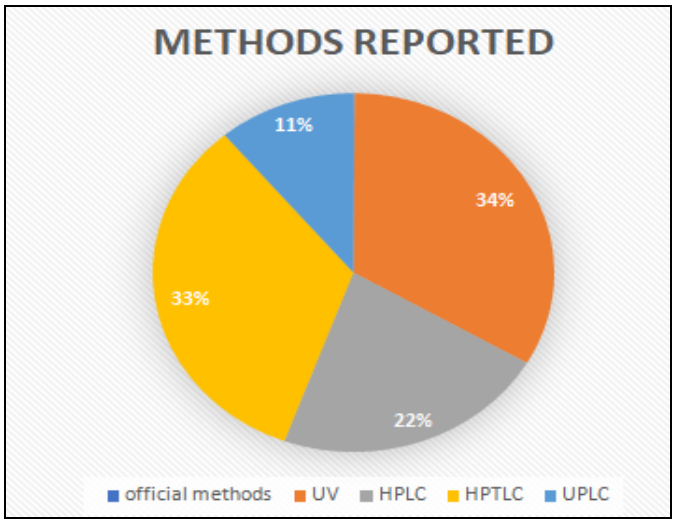

FIG. 4: REPORTED METHODS OF NADIFLOXACIN FROM LITERATURE SURVEY

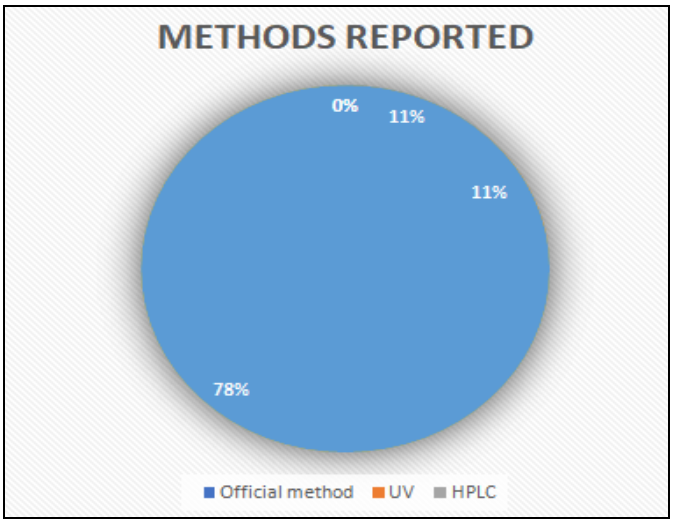

FIG. 5: REPORTED METHODS OF ADAPALENE FROM LITERATURE SURVEY

TABLE 1: REPORTED METHODS FOR NADIFLOXACIN

Sr. no.	Method	Description	Ref.
1	IP 2018	**Column:** 25 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm). **Mobilephase:** A mixture of equal volume of a buffer solution prepared by dissolving 1.927 gm of ammonium acetate in 1000 ml of water, adjusted to pH 3.6 with orthophosphoric acid and acetonitrile. **Wavelength:** 235 nm **Flow Rate:** 1 mL/min **Injection volume:** 10µL.	7
2	Spectrophotometric Estimation of Nadifloxacin in Pharmaceutical Dosage form.	**Solvent:** Methanol **Wavelength:** Absorption maxima - 296.5 nm First order derivative spectrophotometry - 278 nm Area under curve (AUC) - 291-301nm	8

		Linearity: 5 – 25 µg/ml	
3	Development And Validation Of Multiwavelength Method For Simultaneous Estimation Of Nadifloxacin And Ibuprofen In Formulated Hydrogel.	**Solvent:** Methanol **Wavelength:** NAD- 280nm IBU-222nm **Linearity:** 2-20µg/ml	9
4	Analytical method development and validation of Nadifloxacin by HPLC	**Column:** C18 (150 mm x 4.6 mm, 5 µm) **Mobile Phase:** 0.05% Trifluoroaceitic acid : Acetonitrile (65:35 v/v) **Wavelength:** 237 nm **Retention time:**12.3 min **Flow rate:** 1.2 ml/min **Linearity:** 0.03 – 5 µg/ml	10
5	A development and validation of RP-HPLC method for simultaneous estimation of Nadifloxacin and Clobetasol Propionate in its dosage form	**Column:** C18 (250mm X 4.5mm 5µm) **Mobile Phase:** Acetonitrile: Water (50:50 v/v) **Wavelength:** 242 nm **Retention time:** NAD- 2.64min COP- 6.19 min **Flow rate:** 1 ml/min **Linearity:** NAD: 20-240µg/ml COP: 1-12µg/ml	11
6	Simultaneous estimation of Nadifloxacin and Mometasone furoate in topical cream by HPTLC Method.	**Stationary phase:** Silica gel 60 F254 **Mobile phase:** dichloroethane: diethylether: ammonia: methanol: ethylacetate (6:3:0.2:1.75:3.5 v/v/v/v/v) **Wavelength:** 254nm **Rf value:** NAD- 0.12 MOM- 0.85 **Linearity:** NAD- 1000-3000 ng/band MOM- 100-300 ng/band	12
7	Validated HPTLC method for simultaneous determination of Nadifloxacin, Mometasone furoate and Miconazole nitrate cream using fractional factorial design.	**Stationary phase:** Silica gel 60 F254 **Mobile Phase:** Methanol: Ethyl acetate:Toluene:Acetonitrile:3M Ammonium formate in water (1:2.5:6.0:0.3:0.2 v/v/v/vv) **Wavelength:** 224nm **Rf value:** NAD -0.23 MOM -0.70 MIN- 0.59 **Linearity:** NAD-400-2400 ng/band MOM-100-600 ng/band MIN- 400-2400 ng/band	13
8	Validated stability indicating Thin layer chromatographic (TLC) Determination of Nadifloxacin in Microemulsion and bulk drug formulation.	**Stationary Phase:** silica gel 60 F254 **Mobile Phase:** Chloroform : Methanol: Formic acid (7.5 : 2.0 : 0.5 v/v/v) **Wavelength:** 288nm **Rf value:** 0.39 **Linearity:** 50-600µg/ml	14
9	A stability indicating HPTLC method for estimation of Nadifloxacin in topical cream.	**Stationary phase:** silica gel F-650 **Mobile phase:** Chloroform: Methanol: Ammonia (4.3:4.3:1.4 v/v/v) **Wavelength:** 296nm **Rf value:** 0.62 **Linearity:** 50-300ng/band	15
10	Stability indicating UPLC method for the estimation of Nadifloxacin, Terbinafine hydrochloride, Mometasone furoate, Methyl paraben and Propyl paraben.	**Column:** C18 (50mm X 2.1mm ,1.7µm) **Mobile phase:** A) Buffer (pH 3.5): Acetonitrile mixture (95:5 v/v) B) Buffer (pH 3.5): Acetonitrile mixture (25:75 v/v) **Wavelength:** 255nm **Retention time:** NAD-2.6min TER- 6.0 min MOM- 6.9min MP-1.5 min PP-3.4min **Flow rate:**0.4ml/min	16

TABLE 2: REPORTED METHODS FOR ADAPALENE

Sr. no.	Method	Description	Ref.
1	UV spectrophotometric method for determination of Adapalene in bulk and pharmaceutical formulation.	**Solvent:** Methanol **Wavelength:** 237nm **Linearity:** 1-25µg/ml	17
2	Determination of Adapalene in gel formulation by conventional and derivative synchronous fluorometric approaches. Application to stability studies and invitro diffusion test.	**Solvent:** pH 7.0 borate buffer **Wavelength:** First approach- 389nm Second approach- 1.SDSF -346 nm 2.FDSF- 312.45 nm **Linearity:** 2-14µg/ml %Diffusion: 65%	18
3	A new HPLC method for development for cleaning validation of Adapalene active pharma ingredient.	**Column:** C18 (100mm X 4.6mm,3.5µm) **Mobile phase:** Acetronitrile:0.5% Orthophosphoric acid (35:65 v/v) **Wavelength:** 230nm **Retention time:** 4.4min **Linearity:** 2.5-20µg/ml	19
4	HPLC method development and validation for the estimation of Adapalene in pharmaceutical Formulation.	**Column:** C18 (250 X 4.6 mm, 5 µm) **Mobile phase:** Tetrahydrofuran: Acetonitrile: 0.1% Acetic acid in water (20:40:40 v/v/v/v) **Wavelength:** 270nm **Retention time:** 10.44min **Flowrate:** 1.2ml/min **Linearity:** 10-30µg/ml	20
5	Development of analytical method for simultaneous estimation of Adapalene and Benzoyl peroxide in gel formulation by RP-HPLC.	**Column:** C8 (250mm X 4.6mm, 5µm) **Mobile phase:** Acetonitrile: Methanol (90:10 v/v) **Wavelength:** 245nm **Retention time:** ADA- 3.7 min BPO- 5.8min **Flow rate:** 1ml/min **Linearity:** ADA- 1.9-4.4µg/ml BPO- 48-112µg/ml	21
6	Optimization and validation of HPLC for simultaneous determination of Adapalene and Benzoyl peroxide by surface response methodology.	**Column:** C18 (250 X 4.6mm, 5µm) **Mobile phase:** Acetonitrile: Tetrahydrofuran: Trifluoroaceitic acid: Water (21: 16: 0.01: 13 v/v/v/v) **Wavelength:** 270nm **Retention time:** ADA-13.4 min BPO- 3.82min **Flow rate:**1ml/min	22
7	A new RP-HPLC method for estimation of Clindamycin and Adapalene in gel formulation: development and validation consideration.	**Column:** C18 (250 X 4.6mm, 5µm) **Mobile phase:** Acetonitrile: Phosphate buffer Ph 3.0(60:40 v/v) **Wavelength:** 210nm **Retention time:** CP-3.03 min ADA-4.92 min **Flow rate:** 1ml/min **Linearity:** CP -100-500µg/ml ADA- 10-50µg/ml	23
8	A Simple HPLC-DAD	**Column:** C18 (150 X 4.6mm, 5µm)	24

	Method for Determination of Adapalene in Topical Gel Formulation.	**Mobile phase:** Acetonitrile: Water (67:33 v/v) (pH adjusted to 2.5 with OPA) **Wavelength:** 321nm **Retention time:** 6.8min **Flow rate:** 1.4ml/min **Linearity:** 8-16µg/ml	
9	Estimation of Adapalene through isocratic HPLC method in pharmaceutical gel formulation	**Column:** C18 (100 X 4.6mm, 5µm) **Mobile phase:** Acetonitrile: Tetrahydrofuran: Phosphate buffer (pH 2.5 0.01M) (30:40:30 v/v/v) **Wavelength:** 272nm **Retention time:** 2.4 min **Flow rate:** 1.5 ml/min **Linearity:** 14-26 µg/ml	25
10	Method development of accelerated stability study of Adapalene gel by HPLC in Pharmaceutical Formulations.	**Column:** C18 (4.6mm×250mm ,5µm) **Mobile phase:** Acetonitrile: Tetrahydrofuran: Trifluoracetic acid : Water (430:360:210:0.2 v/v/v/v) **Wavelength:** 235nm **Retention time:** 7.910min **Flow rate:** 1ml/min	26
11	Novel Stability Indicating RP-HPLC Method for the Simultaneous Estimation of Clindamycin and Adapalene in Pharmaceutical Dosage Forms.	**Column:** C18 (150mm X 4.6mm) **Mobile phase:** Phosphate buffer (pH3.0): Acetonitrile (55:45 v/v) **Wavelength:** 230nm **Retention time:** CP- 2.84 min ADA- 3.99 min **Flow rate:** 1ml/min **Linearity:** CP- 25-150µg/ml ADA- 2.5-15µg/ml	27
12	Novel Stability-Indicating RP- HPLC Method for the Simultaneous Estimation of Clindamycin Phosphate and Adapalene along with Preservatives in Topical Gel Formulations.	**Column:** C18(50mm X 4.6mm,3.5µm) **Mobile phase:** Ammonium hydrogen Phosphate buffer(pH- 2.50): Acetonitrile (84:16 v/v) **Wavelength:**321nm **Flow rate:** 1ml/min **Linearity:** CP- 20-1500µg/ml ADA- 0.5-150 µg/ml	28
13	Validated stability indicating analytical method for the determination of clindamycin phosphate and adapalene in topical formulation.	**Column:** C18(250 X4.6mm, 5µm) **Mobile phase:** Acetonitrile: Tetrahydrofuran (65:35 v/v) **Wavelength:** 210nm **Retention time:** CP- 4.9min ADA-18.9min **Flow rate:** 1ml/min **Linearity:** CP- 100-300 µg/ml ADA- 10-30 µg/ml	29
14	Development and validation of RP-HPLC method for simultaneous	**Column:**C18 (250mm X 4.6mm , 5µm) **Mobile phase:** Water: Acetonitrile: Tetrahydrofuran : Trifluoracetic acid	30

	determination of Adapalene and Benzoyl peroxide combination Gel.	(29:33:38:0.2 v/v/v/v) **Wavelength:** 270nm **Retention time:** ADA- 4.346 min BPO- 10.066 min **Flowrate:** 1ml/min	
15	A novel method development and validation for related substances of Adapalene in bulk drug product by HPLC.	**Column:** C18 (150 X 4.6mm, 5µm) **Mobile phase:** Methanol: orthophosphoric acid: tetrahydrofuran (55:30:15 v/v/v) **Wavelength:** 260nm **Flowrate:** 1ml/min **Linearity:**20%-200%	31
16	Qualitative and quantitative estimation by HPLC method in Transdermal formulations:	**Column:** C18 (250mm X 4.6mm, 5µm) **Mobile Phase:** Acetonitrile: Tetrahydrofuran: phosphate buffer (30:40:30 v/v/v) **Wavelength:** 272nm **Retention time:** 2.4 min **Flow rate:** 1ml/min **Linearity:** 14-26µg/ml	32

CONCLUSION: This review shows detailed study on the reported Spectroscopic and Chromatographic methods developed and validated for the estimation of Nadifloxacin and Adapalene. Literature review suggest that there are various spectroscopic and chromatographic methods available for the estimation of Nadifloxacin and Adapalene alone and in combination with other drugs. HPLC and HPTLC methods were found to be very common.

There is only one HPLC reported method for Nadifloxacin and Adapalene in their combined dosage form. So, there will be a great scope for the method development and validation of same with good precision, accuracy and robust methods for available marketed combined dosage form of Nadifloxacin and Adapalene.

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CONFLICTS OF INTEREST: Nil

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A REVIEW ARTICLE ON AN EXISTING SCHEDULE M VS REVISED SCHEDULE M

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Keywords:

Guidelines, Computerized, Identification, Qualification, Validation

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ABSTRACT: Schedule M is considered as an important part in the Drugs and Cosmetics Act 1940, Rules 1945. For making a product with proper quality and effective for the human beings it is necessary to maintain or follow the guidelines of schedule M. Schedule M is considered as the guidelines which talks mostly about Good Manufacturing Practices. Schedule M was first established in the year 2001 and it was divided into Part 1 and Part 2. Then in the year 2018 it was divided into 12 Parts more precisely than first one which was established in the year 2001. Then in the year of 2024 it became more precise, and it was divided into 13 Parts and including the changes introduced in, the revised Schedule M which include introduction of a Pharmaceutical Quality System (PQS), Quality Risk Management (QRM), Product Quality Review (PQR), Qualification and Validation of Equipment, and a Computerized Storage system for all drug products. These revised Schedule M will help in making the product proper and effective to the human beings. The revised Schedule M makes it easy for the identification of the risk and to check whether the product is maintaining quality system or not. The revised Schedule M will make the records of the documentation for future references. Schedule M is a crucial part for all the manufacturing products used by the human. Previous Schedule M doesn't give much explanation about each topic which creates problems most of the time. It is better to be revised.

INTRODUCTION: Schedule M is the set of guidelines or regulations which mainly deals with the good manufacturing practices for the pharmaceutical products [1, 2]. It is the part of Drugs and Cosmetics act 1940, rules 1945. It is being followed by all the manufacturers for making a good therapeutic product for the human beings. The products which are made by following the rules or guidelines is effective.

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It is a part of quality assurance system which tells that the products are consistently manufactured, and quality standards appropriate to their intended use. The new schedule M has 13 parts. The existing schedule M only focuses on the good manufacturing practices, but the revised schedule M put a special focus on the premises, plants and equipment with the addition GMP requirements.

In addition, they also focus on the Product quality review (PQR), Pharmaceutical quality system (PQS), Quality risk management (QRM), Qualification and validation of equipment and computerized storage system for all products. It also focuses on the risk management and self-inspection. This will help in producing the drug's safety, quality and efficacy [5, 6]

The revised schedule is more specific to the topic and helps in manufacturing a product with good quality, and effective. As we know that schedule M is the vital part and it is followed by the manufacturers minutely [3, 4].

History: Good manufacturing part of Drugs and Cosmetics Act 1940, was first incorporated in Schedule M of the Drugs and Cosmetics Act & Rules, in the year 1988 and the last amendment was done in June, 2005, deals with Good Manufacturing Practices for pharmaceuticals that should be followed by pharmaceutical manufacturing units in India [7, 8]. Schedule M guides on Good Manufacturing Practices regarding company premises, quality control system, quality check laboratories, production, cleaning of equipment, housekeeping, cross-contamination, and other related topics.

On the last year of 28th December 2023, the revised schedule M was implemented which mostly focuses on the quality management system of the pharmaceutical product [10, 11].

Salient Features:

OLD Schedule M: Schedule M was first divided into 2 parts:

Part 1:

- ✓ Good Manufacturing practices for the premises and materials.
- ✓ It also had a subpart starting from 1A to 1F.

Part II:

- ✓ Requirements of Plant and Equipment:
- External Preparations.
- Oral Liquid Preparations
- Tablets
- Powders
- Capsules
- Surgical Dressing
- Ophthalmic Preparations
- Pressurizes and suppositories
- Inhalers and vitrallae
- Repacking of Drugs and Pharmaceutical Chemicals
- Parenteral Preparation

Proposed Schedule M: Schedule M was divided into 12 parts:

Part I: Good Manufacturing Practices for Pharmaceutical Products.

- ✓ Part I is completely different.
- ✓ This Part I is termed as “Main Principles” & it is mandatory to follow irrespective of product category.
- ✓ An Appendix I which deals with requirements of Site Master File.

Part II to Part XII:

- ✓ Specified requirements for manufacturing, as per product categories. E.g. Sterile products.
- ✓ Oral Solid dosage Forms etc.
- ✓ Five new categories are added as compared to existing Schedule M.

Part XIII:

- ✓ Requirements of plant and equipment for manufacturing of 11 categories of pharma products.
- ✓ This section is similar as of previous schedule M 2001.

New Schdeule M: Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products

Part I:

- ✓ Pharmaceutical Quality system
- ✓ Quality Risk Management
- ✓ Good Manufacturing practices for pharmaceutical products.
- ✓ Sanitation and Hygiene

- ✓ Qualification and Validation.
- ✓ Complaints and Adverse Reaction
- ✓ Product Recall
- ✓ Change Control
- ✓ Production under loan license or contract and contract analysis and other activities.
- ✓ Self-inspection, quality audits and supplier audits and approval
- ✓ Personnel
- ✓ Premises
- ✓ Equipment
- ✓ Materials
- ✓ Reference standards
- ✓ Waste materials.
- ✓ Documentation
- ✓ Good practices in production
- ✓ Good practices in quality control
- ✓ Computerized system

Appendix -1: Site master file.

Part II to Part XII:

- ✓ Part II- Specific requirements for manufacture of Sterile Products, Small & Large Volume Parentals, Ophthalmic Preparations.
- ✓ Part III Specific requirements for manufacture of Hazardous substances such as Sex Hormones, Steroids or Cytotoxic substances (Newly Added).
- ✓ Part IV Specific requirements for manufacture of Biological Products (Newly Added).
- ✓ Part V Specific requirements for manufacture of Radiopharmaceutical Products (Newly Added).
- ✓ Part VI Specific requirements for manufacture of Phytopharmaceutical Products (Newly Added).
- ✓ Part VII Specific requirements for manufacture of Investigational Pharmaceutical Products for Clinical Trials in Human (Newly Added).
- ✓ Part VII Specific requirements for manufacture of Oral Solid Dosage Forms.
- ✓ Part IX Specific requirements for manufacture of Oral Liquids.
- ✓ Part X Specific requirements for manufacture of External Preparations.
- ✓ Part XI Specific requirements for manufacture of Metered Dose-Inhalers.
- ✓ Part XII Specific requirements for manufacture of Active Pharmaceutical Ingredient.

Part XIII:

1. Requirements of Plant and Equipment for External Preparations.
2. Requirements of Plant and Equipment for Oral Liquid Preparations.
3. Requirements of Plant and Equipment for Tablets.
4. Requirements of Plant and Equipment for Powders.
5. Requirements of Plant and Equipment for Capsules.
6. Requirements of Plant and Equipment for Surgical Dressing.
7. Requirements of Plant and Equipment for Ophthalmic Preparations.
8. Requirements of Plant and Equipment for Pessaries and Suppositories.
9. Requirements of Plant and Equipment for Inhalers and Vitrallae.
10. Requirements of Plant and Equipment for Repacking of Drugs and Pharmaceutical Chemicals.
11. Requirements of Plant and Equipment for Parental Preparation.

New Schedule M Principles:

Pharmaceutical Quality System (PQS): It is a part of pharmaceutical Management system in a pharmaceutical Industry. Pharmaceutical quality system should be applied to the product starting from the manufacturing of the product to the dispatch of the product to the market [13]. In every manufacturing company the senior management responsibility is to implement an effective PQS in the company. The finished product should be checked and confirmed then only they are dispatched. The CAPA (Corrective action and preventive action) should be maintained so that any problem is there with the product then it can be identified by the root cause analysis so that the problem does not occur in the future [15].

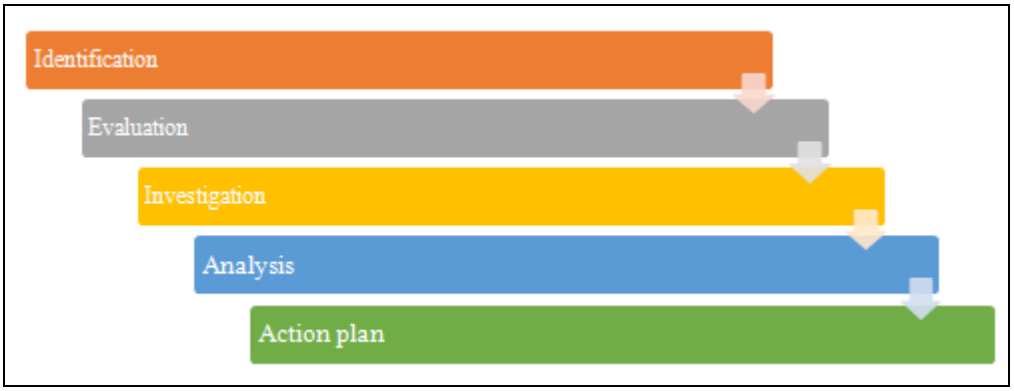

FIG. 1: FLOW CHART OF CAPA PROCESS

There should be also quality risk management for identifying the risk. Any defect, deviations or other problems should be reported, investigated and recorded. The self- inspection or audit should be done in each step so that the mistake can be overcome [17].

The aim of the Pharmaceutical Quality Management System (QMS) is to guarantee and uphold consistent and superior quality in the manufacturing of pharmaceutical products through an all-encompassing set of guidelines, protocols, and practices [18].

Quality Risk Management: It is the specific tool to assess the risk or the defects associated with the manufacturing of the product and drug substances. If we can overcome the risks associated with the product then we can provide a quality product [17].

There is always some danger involved in the production and use of medication (medical) products, including their constituent parts. The whole risk consists of more than just the risk to its quality.

It's critical to realize that good risk-based decision-making throughout the product lifetime ensures that the qualities critical to the medication (or medicinal) product's quality are preserved and that the product continues to be safe and effective [16].

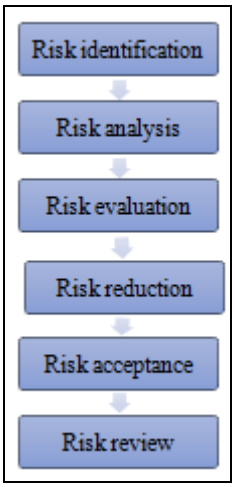

FIG. 2: FLOW CHART OF RISK IDENTIFICATION PROCESS

Product Quality Review: It is necessary to carry out rolling, periodic, or regular quality reviews of all pharmaceutical items. Check that the quality parameters and product process are consistent. Based on the quality review report, the manufacturer should determine whether re-validation or the relevant CAPA is required. CAPAs must be finished on time and include an ongoing evaluation of their efficacy [14].

In addition to making sure the data is accurate, the person in charge of product release should make sure the quality review is finished in the allotted time. Every year, product quality reviews must be carried out and recorded [13].

Every annual review report must also take into account all of the prior reviews.

The report should address a few of the following topics, but not all of them:

- ✓ Examination of the product's raw components and packaging materials.
- ✓ Examining the traceability of active ingredients in the supply chain.
- ✓ Examination of crucial process controls and final product outcomes a study and inquiry of every batch that didn't match the specified specifications.
- ✓ An examination of all modifications made to the procedures or analytical techniques.
- ✓ An examination of the filed, approved, or rejected dossier variations.
- ✓ An analysis of the stability monitoring program's findings and any unfavorable patterns.

Sanitation and Hygiene: Strict standards of hygiene and sanitation must be followed in all facets of the pharmaceutical manufacturing process. The scope of hygiene and sanitation should include Employees, Facilities, Containers, Production Materials, Equipment and Cleaning and Disinfecting Products. Anything that comes into contact with the merchandise [15]. It is necessary to remove any potential sources of contamination. There should be a sanitization and hygiene program in place. Wash hands with soap and water [13]. The dress should be clean or else it would cause cross contamination to the product. The personnel who are involved in the manufacturing industry should be free from any kind of diseases.

The Qualification and Validation: The updated schedule M lists more precise requirements than the previous one did. The equipment, instruments, processes, and procedures that the company wants qualified and validated should be identified. There should be a validation master plan in place outlining the essential components of validation and qualification program [14]. It is actually used to establish and proof design Qualification (DQ), installation qualification, performance qualification (PQ) / process, operations qualification (OQ), and qualification (IQ) verification (PV). Re-qualification and re-validation requirements must be specified precisely [15]. The accountability for carrying out validation activities needs to be specified explicitly. Special consideration must be given to the validation of automated systems, analytical test methodologies, and methods for cleaning. It is also playing an important role in manufacturing of the product [16].

Production under Loan License or Contract and Contract Analysis and Other Activities: One of Schedule M's most significant additions. To prevent quality problems, activities carried out under a specific arrangement and covered by GMP should be precisely defined, agreed upon, and crucially controlled. The following tasks, including but not limited to tech transfer, supply chain, subcontracting validation, batch releasing authorization, changes or changes resulting from incidents or errors, quality control, in-process controls, *etc*., should be covered by a quality contract or agreement [19].

Continual the vendor's contract acceptor conducting an audit of the site(s) should be cognizant of all the hazards related to the product, work, or tests that could endanger persons, property, equipment, *etc*. Competent individuals with the necessary understanding of process technology, analysis, and good manufacturing practices should develop the contract's technical provisions.

Computerised System: Very significant section regarding the regulatory agencies' present strategy. The qualification, validation, review, and data management related to computerized systems are covered in detail in this section. Validation needs to be grounded in the system's complexity, diversity, and criticality. Any modifications to the electronic system must follow a change procedure with upholding and approving each and every record. These documents will show that the system is kept up to date and validated [18]. There must be a backup system in place to ensure that documents are never permanently lost because of failure or collapse of the system. Computerized systems must be equipped with sufficient safeguards against unwanted access or modifications to the data.

Waste Materials: Waste materials must be stored properly and safely in a designated area. It is necessary to properly segregate waste materials from one another. Combustible and toxic products must be stored in appropriately designed, independent, closed cabinets. The removal of solid, liquid, and gaseous effluents and sewage. The manufacturing area must adhere to the specifications of Board for Environment Pollution Control. All biomedical waste needs to be eliminated in accordance with the guidelines of the Biomedical Waste Products. Fumigating agents, insecticides, rodenticides, and sanitizing supplies not allowed to contaminate tools, supplies for starting, materials used in packaging, manufacturing processes, or final goods. Waste materials should be put in the dustbin for the better use.

TABLE 1: COMPARISON BETWEEN SCHEDULE M AND REVISED SCHEDULE M

S. no.	Point	Existing	Updated
1	Sanitation	It covers only workers/ manufacturing premises	It covers personnel, equipment, production materials, manufacturing area, containers, closure systems
2	Qualification/ Validation	It covers only manufacturing process, testing and cleaning	It covers premises, utilities and equipment.
3	Product Recall	There was no provision to inform the LA.	Should be informed to LA, Comprehensive system specifies for prompt and effective recall.
4	Compliance and Adverse drug reaction	Serious adverse drug reactions	This includes faulty manufacturer, product deterioration, serious quality problems.
5	Change control	Only in case of significant change	This covers changes in specifications, analytical methods, facilities, utilities, equipment, labeling and packaging
6	Production	No details of contract giver, acceptor was required	This covers the roles and responsibilities of contract giver, acceptor agreement.
7	Self-inspection/ quality audit/ supplier audit/ approval	Routinely performed and also in specific occasion, i.e. during recall and during third party inspection	At least once a year, supplier audit and approval
8	Materials	-	Validated computerized storage system. Identify test for each container except dedicated facilities, reworking of rejected products- new batch number, part of earlier batches into a batch of the same product at defined stage of manufacturer. Extension of retest date.
9	Reference standard	-	IP RS/IS procured from IPC procedure for working standard.
10	Documentation	Master Formula Record (MFR), Standard Operating Procedure (SOP) in hard copy for verification	Audit trail to ensure existence of documented evidence, traceability, MFR- hold time permitted for intermediates and in-process materials.
11	Sterile products	Requirement has been provided in schedule M but without reference to latest requirement.	Separate comprehensive provisions on specific requirements
12	Hazardous materials, hormones, steroids, cytotoxic	No separate provision about requirement for manufacturing of such product however segregated/isolated production areas within building with different AHU and pressure differential	Separate comprehensive provisions on separate requirements.
13	Biological,V-Radiopharmaceutical, clinical trials	No such separate provision about requirement for manufacturing of such product	Separate comprehensive provisions on separate requirements.
14	Pharmaceutical Quality system (PQS)	No section in existing schedule M	Newly added. Specific requirements are mentioned separately
15	Quality Risk Management	Not mentioned in existing schedule M	Separate section for risk management systems

CONCLUSION: It is concluded that the new or the existing schedule M is very useful for the pharmaceutical industry in manufacturing a product. The existing schedule M is fully explained

than the revised schedule M. Existing Schedule M had 12 parts but the new schedule M is 13 parts and it is more precise. As we know that schedule M mostly talks about good manufacturing practices. Existing schedule M doesn't include the requirements of the radiopharmaceuticals, phyto-pharmaceuticals, investigational Pharmaceutical products used in the clinical trials. Proper schedule m will help in making a good pharmaceutical product along with maintaining a safety, quality and efficacy.

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AYURVEDIC INTERVENTIONS FOR MALNUTRITION: ENHANCING INDIA'S NUTRITION PROGRAMS FOR CHILDREN

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ABSTRACT: Malnutrition continues to be a significant public health concern, affecting the survival, growth, and well-being of both current and future generations, especially in developing nations such as India. This study examines the intricate characteristics of malnutrition, including insufficient and excessive nutrition, with a major emphasis on protein-energy malnutrition (PEM) in children, the high occurrence of stunting, wasting, and underweight conditions in children, based on data from the National Family Health Survey (NFHS-5) and multiple studies conducted in Jaipur. It emphasizes the notable gender discrepancies and socio-economic factors contributing to these conditions. Ayurveda emphasizes the significance of maintaining a well-balanced diet (*Aahara*) and recognizes the influence of *Vata dosha* in disturbing the process of digestion and absorption of nutrients, resulting in ailments like *Karshya*, *Balashosha*, and associated disorders. Ayurvedic therapies prioritize dietary alterations, herbal supplementation, and lifestyle adjustments to restore physiological equilibrium and enhance overall well-being. This article suggests incorporating Ayurvedic concepts into current government nutrition initiatives, such as POSHAN Abhiyaan and Pradhan Mantri Matru Vandana Yojana (PMMVY). Concrete suggestions encompass prenatal and postnatal care measures, guidelines for infant and toddler nutrition, and Ayurvedic therapeutic therapies aimed at improving maternal and child health outcomes. The integration includes customized nutrition regimens, prenatal yoga, herbal assistance, and educational workshops to promote comprehensive well-being. By integrating Ayurvedic principles with contemporary nutrition programs, this approach presents a hopeful plan to address the malnutrition epidemic in India by promoting long-term health and well-being, making a significant contribution to national development and the progress of public health.

INTRODUCTION: Growth and development are intimately correlated with nutrition. The greatest growth and development will occur throughout childhood. A child must receive appropriate nutrition supplements to meet the growing body's calorific needs.[1]

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Malnutrition, particularly protein energy malnutrition (PEM), poses significant challenges for children, exacerbated by various factors including poor habits and socio-economic issues. Malnutrition is referred to as a silent emergency [2].

The term malnutrition encompasses excessive and insufficient nourishment, ranging from severe dietary deficits to obesity [3]. Approximately 155 million children (22.9%) and 52 million children (7.7%) worldwide are wasted and stunted, respectively. Children under five are becoming less nourished, with 11 out of 17 states experiencing a rise in stunting or chronic malnutrition, defined as

low height relative to age. Thirteen out of 17 states have seen an increase in severely wasted youngsters, a condition known as acute malnutrition or wasting. At least 40% of children under five in Gujarat and Bihar are underweight, highlighting the need for improved nutrition and health outcomes for these vulnerable children [4]. 36% of children under age five years are stunted (short for their age); 19 percent are wasted (thin for their height); 32 percent are underweight (thin for their age); and 3 percent are overweight (heavy for their height) [5].

Malnutrition is mostly caused by a poor diet and recurrent infections, which result in insufficient protein intake, carbohydrates, fats, and minerals. Children who are undernourished are more likely to experience severe and frequent infectious infections; even modest undernutrition raises the risk of morbidity and mortality in children. Long-term developmental issues in children can also result from chronic undernutrition. Undernutrition symptoms include thinning and dry hair, moon face, low sleep, pituitary hormone abnormalities, thyroid function changes, low body temperature, heart fat loss, lightheadedness, slow heart rate, mild anemia, fine-raised white hair, constipation, amenorrhea, brittle nails, subcutaneous fat loss, diminished muscle mass, dry skin, slower reflux, and edema [6].

According to ancient Ayurvedic texts, one of the *Trayopsthambha* of life is *Aahara* (food) [7]. *Ahara, Viharaja*, and *Mansika* are the causes of undernutrition, according to Ayurveda. Energy production and the maintenance of living tissues are the two primary objectives of the *Aahara*. *Vata dosha* is the primary element to make children malnourished. Vitiated *vata* results in *Rukshta* and *Agni mandyata* that proceeds to cause improper digestion of food. This leads to emaciation in children as the body will not get appropriate nutrients. Emaciation of body fat and muscles results from undernutrition, which vitiates bodily tissues, causes dryness, and interferes with their ability to absorb nutrients [8]. The primary risk factor for this condition is *Ahara Dosha*; in particular, erroneous intake habits called *Alpasana* and *Vishamasana* lead to the development of *Karshya*. *Karshya* is a *Vata-Pradhan Aptarpanjanya Vyadhi* [9]. Malnutrition is referred to in Ayurveda as *Apatarpanjanya Vyadhis* [10]. These conditions can be classified as *Karshya, Phakka, Parigarbhika*, and *Balashosha* depending on their severity and cause.

Prevalence of Malnutrition in Jaipur:

1. A cross-sectional study on 1007 under 5-year children, was conducted by Sharma et al in 2021 in Jaipur, and they found that 22.8% of children were malnourished [11].

2. Gupta *et al* in their record-based retrospective analytical observational study which was conducted in Jaipur in the year 2023, found that 86% of children out of 264 enrolled malnourished children were below 2 years of age group [12].

3. Pragati Chaudhary *et al.* conducted a community-based cross-sectional study from 2016 to 2017 in a slum area of Jaipur city, Rajasthan. A total of 2007 children aged 6-59 months were selected for the study. Among the screened children, 35.7% were found to be underweight, 43% were stunted, and 10.5% were wasted. Additionally, 2.5% of the children had severe acute wasting, and 8.0% had moderate acute wasting [13].

Different Disorders can be Corelated to Malnutrition in Ayurveda:

***Karshya*:** It is a condition characterized by excessive emaciation, caused by factors such as a fat-free diet, excessive fasting, inadequate food intake, over-administering of *Sanshodhan* treatment or *Panchkarma* procedures, *Shoka, Ruksha udvartan, Krodha, Ativyayam, etc*.

Clinical features include *Daurbalya, Dhamani-jaladarshanam, Sthula parva, Nidra nasha, Shushka-sphika- udara-griva.* Excessive emaciation can lead to *Pleeharoga, Kasa, Kshaya, Shwasa, Gulma, Arsha, Udara roga, Grahani roga* [14].

Principle of Treatment [15]: Acharya Charak has advised *Brimhana* and *Laghu Santarpan*.

1. *Daivyapashray- Gandha Malya Dharan.*

2. *Yuktivyapashray- Nava anna, Nava Madhya, Gramya-anupa-audakamansa rasa, Dadhi,*

Sarpi, shali, masha, godhuma, gud-vaikrit, Basti, Taila abhyanga, Udwartan, timely *dosha-avasechan, rasayan.*

3. *Satvavjaya- Swapna, Harsha, Sukh shaiyya, Chinta viram, Priya darshan.*

***Balashosha*:** *Balashosha* is only described by *Acharya Vagbhatta* in his books *Astangasangraha* and *Astangahridaya*. Other *Acharya* like *Charak* and *Sushruta* discussed the term '*Shosha'* and '*Krusha', Sharangadhara* named it '*Gatrashosha'* and '*Daurbalya'* and *Yogaratnakara* termed it '*Karshyaroga'* [16].

Ashtang Hridaya [17] and *Ashtang Sangrahya* [18] describe symptoms of *Bala Shosha*, including *Arochaka, Pratishyaya, Jwara, Kasa, Shosha, Snigdha mukha, Snigdha netra, Suklamukha, and Suklanetra.*

Principle of Treatment: *Acharya Vagbhatta* provides a comprehensive treatment plan for *Balashosha*, with a focus on addressing the root reasons, balancing the *Dosha*, and rejuvenating *Agni* at every level. The treatment is divided into two categories: one for the mother (*Dhatri*) and the other for the child.

Treatment for Mother: In *Ksheerapa* and *Ksheerannada*, breastfeeding is the mother's primary source of nourishment for her child. However, imbalanced doshas can impact the child's health. To prevent this, the mother should follow three steps: 1) *Nidana Parivarjana*, which prioritizes prevention over cure, 2) *Samsodhan Chikitsa*, which treats impaired or corrupted breast milk, and 3) *Samsarjana karma*, which includes a healthy and nutritious diet and the use of "*Stanya Sodhaka"* and "*Stanya Janana*" medications.

Acharya Kashyapa classifies *Pathadi* and *Patoladigana* as "*Stanya Sodhaka" gana*, while *Acharya Charaka* recommends medications with *Tikta, Kashaya, Katu*, and *Madhura* tastes for *Stanya Shodhana*. The *Stanya Shodhaka Dasemani* formula includes *Patha, Shunthi, Devdaru, Musta, Murva, Guduchi, Kutaja, Kiratatikta, katurohini,* and *Sariva.*

Treatment for Children: Ayurvedic treatment for children includes multiple modalities, including *Nidana Parivarjana, Samshodhana*, and *Basti* treatment. In *Balashoshaa*, the *Amarasa* creation occurs due to the deterioration of *Jatharagni* states, leading to *srotasa* obstruction and increased *Kapha dosha*. *Deepana-Pachana* medicines, such as *Chitraka*, help disrupt the pathogenesis of *Balashoshaa. Balashoshaa* treatment prioritizes clean air, sunlight, proper cleanliness, and loving attention. *Aushadhi Chikitsa*, *Anupana*, powdered medications, and *Aushadha* can be used to treat *Balashoshaa*. Malnourished children and individuals with anorexia can also be treated using various herbal remedies and powdered substances.

Dusthaand Kshina Stanya: Nutritional deficit in children aged up to 1 year, known as *Ksheerapa*, is primarily caused by inadequate food or a lack of breast milk (referred to as *Kshina Stanya* or *Stanya Kshaya*). Malnutrition causes a decrease in both the amount and quality of breastfeeding, leading to insufficient production of bodily tissues (*Dhatus*) and imbalance of the *Vata dosha* [19]. As a result, this causes irregular digestion and extreme thinness. The *Kapha Dosha* [20], which is responsible for the growth and development of children, might be further weakened if it is already weakened.

***Sushka Revati* [21]:** The condition is characterized by a gradual wasting away of all bodily parts, accompanied by symptoms such as diarrhea, loss of appetite, changes in the skin, swollen nodules in the abdomen, and a condition known as geographic tongue. Personal hygiene procedures like as anointment, bathing, fumigation, seclusion, and cleaning of surrounds are employed to control it. Several medications such as *Swarna Basant Malti, Shilajatvadi Lauha, Shringa Bhasma, Vardhaman Pippali,* and medicated *Ghrita* are recommended.

Phakka Roga: *Phakka* is a term used to describe slow movement in children due to inadequate physical growth and alterations in psychomotor function. It is categorized into three groups: *Kshiraja Phakka, Garbhaja Phakka*, and *Vyadhija Phakka. Kshiraja Phakka* refers to malnutrition during infancy, while *Garbhaja Phakka* is a complication arising from various infant disorders. *Vyadhija Phakka* is marked by extreme malnourishment, weak limbs, subcutaneous fat mobilization, increased stool and urination

frequency, irritability. The chapter "*Phakka Chikitsa Adhyaya* [22]" by Acharya *Kashyapa* discusses the treatment of *Phakkaroga* by balancing the *Kapha* and *Vatadoshas*. The treatment can be divided into two main categories: one for *Dhatri* (wet nurse) and the other for *Balaka* (child). The severity of *Stanya* vitiation in *Dhatri* is caused by *Kapha Dosha*, resulting in symptoms like *Jadatva*, *Mukatva*, and *Pangutva Samprapti*. Agnimandya, caused by *Samprapti Vighatan*, *Dushta Stanya*, *Stanyabhava*, and other ailments, leads to undernourished *Dhatu*, resulting in a frail and malnourished body in infants.

TABLE 1: PREVIOUS CLINICAL STUDIES

S. no.	Author	Journal Name	Title and Year	Study type, Interventional groups, Route, Anupam,	Findings
1	Renu B Rathi *et al* [23]	International Journal of Ayurvedic Medicine	A comparative study on the effectiveness of *Pathadichurna* and Protein powder in *Karshya* (Undernutrition) among preschool children 2023	Randomized parallel group open label, N=30, Group A-15, *Pathadichurna*with one cup of milk, Group B-15, Protein powder with one cup of milk	With *Pathadichurna,* 66.67% of weight gain has been seen, while with Protein powder 60% of weight gain has been seen.
2	Neha Vats *et al* [24]	Ayushdhara-An International Journal of Research in AYUSH and Allied Systems	A clinical study to evaluate the effect of *karshyahar yoga* granules and *ksheerbalatailaMatra Basti* in *karshya*w.s.r to undernutrition in children 2022	Open label, N=40 *karshyahar yoga* granules-130 mg/kg bd with milk & honey, *ksheerbalataila Matra Basti*- according to age, Age (years) -Dose 1. 2-3 - 15ml 2. 4-5 - 20ml 3. 6-11 - 40ml 4. 12-16 - 80ml	12.5% patients showed marked improvement, 42.5% patients showed moderate improvement and 45% patients showed mild improvement. No adverse effect of the trial drug was observed during the study
3	Sagar *et al* [25]	International Ayurvedic Medical Journal	Ayurvedic understanding and management of *Karshya* (malnutrition) in children: A case report. 2019	Case study N=01	Significant changes were found in different parameters, including body weight, bowel status, generalized weakness etc., after 10 days of treatment.
4	Bhagyashre *et al* [26]	Indian Journal of Applied Research	Effectiveness of ayurvedic nutritious therapy in prevention and management of malnutrition, illness reduction and health improvement of mothers and children. 2019	Randomized control trial N=2054 (1035-case, 1019-control), 4 groups A. 6 months-1 year child- 2.5 gm - ayurvedic kalp -twice a day. B. 1–3-year child- 2.5 gm - ayurvedic kalp - twice a day, 1 biscuit -5 gm - once a day. C. 3-6 years children- 2.5 gm ayurvedic kalp and 1 biscuit - 5 gm twice daily. D. In women- 5 gm kalpa, 2 biscuits twice daily.	It was found that, weight has been significantly increased (case-97.1%, control-82.2 %) Nutritional- increased (case-40%, control- 8.4 %) Hb%- increased (case-91%, control-36.51%)
5	Firke AR *et al* [27]	Journal of Ayurvedic and Herbal Medicine	An Exploratory Clinical Trial to Evaluate Efficacy of *Kushmanda*(Benincasa hispida) for weight gain in Malnourished Children. Journal of Ayurvedic and Herbal Medicine 2019	An open end, randomized, controlled clinical study 2 groups a. *Kushmandkalpa* with regular diet, 10gm b. Regular diet only	It has been found that the therapy used in the trial group, i.e. *Kushmandakalpa*, is more effective in increasing weight than the regular standard diet group
6	Kamlesh mali *et al* [28]	International Journal of Novel Research and development	Ayurvedic Management of Karshya -A case Report 2023	A Single case study N=01 *Dashmooladilehya*- 2 teaspoon with *Sukhousnajala*; 3 times a day, diet (*Ahara*) &	Significant improvement was seen as after treatment of one month there was 25.1 kg weight as compared to before treatment which was 22.8 kg. *Greeva* &

		(IJNRD)		*Vihara* was planned	*Udara* circumference also increase post one month treatment.
7	Raj kumar *et al* [29]	International Journal of Research in Academic World	Role of Mashadi Yoga in the Management of Balashosha with Special Reference to Protein-Energy Malnutrition in Children: A Randomized Controlled Trial 2024	A Randomized Controlled Trial N=40(20 in each group) 2 groups a. *Mashadi yoga* A b. *Mashadi yoga* B	*Mashadi yoga* B was more effective than *Mashadi yoga* A.
8	Arun Raj GR *et al* [30]	International Journal of Research in Ayurveda Pharmacy	Effectiveness of Ayurveda intervention in the management of *Karshya* (Grade I and II Under Nutrition) in children 2019	A clinical study N=27 2 groups a. Study group 1. Deworming 2. Chitrakadivati ½ BD for 3 days 3. Amritprashaghrita 6ml BD b. Home-based food along with 1. milk-150 ml 2. Seasonal fruit-1or2 3. egg - 1	The study group showed a statistically significant result in improving children's weight with *Karshya* than the control group. *AmritapraashaGhrita* is effective in improving weight and in reducing the associated complaints of *Karshya* like *Dourbalya* (general weakness) and improving *Kshudha* (appetite), *Cheshta* (interest in activities) and *Aakruti* (appearance)
9	Dinesh ram *et al.* [31]	World Journal of Pharmaceutical and Medical Research.	Clinical study to evaluate the efficacy of *ashwagandhamodaka* in *karshya* 2020.	A clinical study N=30 *Ashwagandha Modaka* orally	*Ashwagandha Modaka* has a *Madhura Vipaka* and exhibits *Laghu* and *Snigdha* qualities. These properties contribute to an increase in *Kapha* dosha in the body, making *Ashwagandha Modaka* particularly beneficial in managing *Karshya* (emaciation or undernourishment).
10	Divya S. Gupta *et al* [32]	International Journal of Pharmaceutical Research and Applications 2022	An Approach towardsManagement of *Balshosha*(Moderate Acute Malnutrition) by Ayurveda regimen- A Single Case Study 2022	A single case study N=01 *Lashunadivati* 125 mg for 7 days with luke warm water *Chaturjatisambharak*4 gm BD with *ghrita* for 28 days RUTF+otherdiet for 28 days	Improvement was seen in terms of weight, height & MAC. Weight before treatment was 10 kg and after treatment was 10.8 kg, while height was 86 cm before treatment and 87.3 cm after treatment. MAC increased from 13 cm to 13.5 cm.
11	Dhanawade *et al* [33]	International journal of research in Ayurveda and medical sciences	To study the effect of *Shatavaryadichurna* in *balakarshya*w.s.r. to under-weight children 2019	An open randomized controlled trial design N=30 2 groups a. *Shatavaryadichurna* b. *Vidaryadichurna*	*ShatavaryadiChurna* provides greater relief than *VidaryadiChurna* in symptoms like weight gain, loss of appetite (*Kshudhamandhya*), and mid-upper arm circumference (MUAC) in cases of *Balkarshya* (childhood malnutrition). However, in terms of *DhamanijalaPradarshan* (visible veins), both groups showed equal effectiveness

Malnutrition, often known as *Karshya*, is a state marked by a sequence of physiological disturbances. The main dosha implicated is *Vata*, which can be exacerbated by circumstances such as inadequate food, stress, and excessive physical exertion. *Pitta* and *Kaphadoshas* may also have an influence. When *Vata* aggravation occurs, it impairs *Agni*, which is responsible for digestion and metabolism. This impairment leads to difficulties in digestion and the absorption of nutrients. When *Agni* is not functioning properly, it leads to the creation of *Ama*, which blocks the digestive pathways and hinders the absorption of nutrients. Dysfunctional *Agni* disrupts tissue metabolism, resulting in insufficient feeding of bodily tissues, specifically muscle and adipose tissue. *Ama* and an imbalanced *Vata dosha* obstruct the body's pathways, leading to nutrient

insufficiency and subsequent weight loss. *Karshya* is characterized by the presence of symptoms such as extreme thinness, weakness, reduced desire to eat, dry skin, and overall physical weakness.

Government Schemes for Combating Malnutrition: The Government has accorded high priority to the issue of malnutrition and is implementing several schemes/programs of different Ministries/Departments through States/UTs to address various aspects related to nutrition. The Ministry of WCD is implementing POSHAN Abhiyaan, 'Pradhan Mantri Matru Vandana Yojana', Anganwadi Services and Scheme for Adolescent Girls under the Umbrella Integrated Child Development Services Scheme as direct targeted interventions to address the problem of malnutrition in the country including the State of Rajasthan. Under the Anganwadi Services of the Umbrella ICDS Scheme, Supplementary Nutrition is provided to children under 6 years of age in the form of Take-Home Ration, Morning Snacks and Hot Cooked Meals as per the provisions of the National Food Security Act, 2013. The Supplementary Nutrition is provided to bridge the gap between the Recommended Dietary Allowances (RDA) and the Average Daily Intake (ADI) among this age group as per the nutritional norms provided under Schedule II of the Act. Severely malnourished children are provided additional nutrition in the form of food supplements providing 800 Kcal of energy and 20-25 g of protein [34].

DISCUSSION: Malnutrition remains a significant public health challenge, especially in developing nations like India. This condition, encompassing both undernutrition and overnutrition, detrimentally impacts children's immune systems and mental development, contributing to high rates of infant and child mortality. Protein-energy malnutrition (PEM), a prevalent form of undernutrition, is particularly concerning as it leads to various health complications. In India, the prevalence of malnutrition is alarming, with numerous children suffering from stunting, wasting, and being underweight, as highlighted by the National Family Health Survey (NFHS-4). These conditions are predominantly driven by inadequate diets and recurrent infections, resulting in insufficient intake of essential nutrients. Ayurveda, an ancient system of medicine, offers valuable insights into addressing malnutrition. According to Ayurvedic principles, factors like improper diet and lifestyle choices contribute to conditions like *Karshya*, *Balashosha*, and other related disorders. Ayurvedic texts emphasize the significance of a balanced diet (*Ahara*) and suggest that imbalances in Vata dosha can lead to malnutrition by impairing digestion and nutrient absorption. Ayurvedic treatments focus on holistic approaches, including dietary modifications, herbal supplements, and lifestyle interventions, to restore balance and promote optimal health.

Malnutrition, mostly caused by *Vata*, can be alleviated by the use of different herbs and practices. Herbs infused with *Guru, Shlakshan*, *Ushna*, *Pichila*, and *Guna* are employed to allievate *Vata*. *Deepana* and *Pachana* substances are utilized to augment *Agni*. To rectify *Rasavahasrotodushti*, *Langhanchikitsa* is indicated. *Balya* and *Brimhana Chikitsa* are therapeutic approaches aimed at addressing conditions such as *Daurbalyata (*weakness*), Oja kshaya* (depletion of vital essence), and stunted stature along with low body mass. *Nidana Parivarjana* encompasses changes in nutrition, lifestyle, and dietary interventions. *Ahara* encompasses a nourishing diet that include easily digestible foods like as milk, ghee, fruits, vegetables, whole grains, and pulses.

Medhya Rasayana incorporates cognitive-enhancing herbs such as *Brahmi* and *Shankhapushpi* to improve memory and cognition. *Vihara* encompasses a daily regimen that includes sufficient rest, physical activity, and methods for relaxing. Engaging in *Yoga* and *Pranayama* exercises helps aid digestion, alleviate stress, and promote general well-being. Herbal medications encompass *Balya* and *Brimhana* herbs, *Agni Deepana* and *AmaPachana*, as well as *Panchakarma*, which refers to cleansing therapy. *Rasayana* Therapy utilizes revitalizing herbs and formulations such as *Chyawanprash* and *Triphala*. Tonics are specialized remedies designed to enhance the body's immune system and promote optimal feeding of tissues. In Jaipur, the prevalence of malnutrition among children is notably high, with significant percentages suffering from varying degrees of underweight, stunting, and wasting.

Studies indicate that malnutrition rates are higher among female children compared to males, underscoring the need for targeted interventions. These interventions should address both the immediate nutritional needs and the underlying socio-economic factors contributing to malnutrition.

Integrating Ayurvedic principles into existing government nutrition programs can significantly enhance their effectiveness. Initiatives like POSHAN Abhiyaan and Pradhan Mantri Matru Vandana Yojana (PMMVY) can incorporate Ayurvedic dietary plans, prenatal yoga, and herbal support to improve maternal and child health outcomes.

Anganwadi centers can offer Ayurvedic-inspired meals and snacks, along with herbal liquids such as decoctions of specific medicines, specific *Yusha/Ksheerpak* preparations *etc*. indicated in *Karshya Chikitsa, Rasayan* and *Brimhana* formulations, to provide holistic nutritional support. For adolescent girls, personalized nutrition plans and workshops on Ayurvedic lifestyle practices can address specific needs related to growth, development, and menstrual health.

Implementing Ayurveda to Address Malnutrition:

Antenatal Care:

Ayurvedic Dietary Guidelines for Pregnant Women: Promote a well-rounded diet which is abundant in whole grains, vegetables, fruits and dairy products. Incorporate *Garbhini Paricharya.* It includes month wise dietary plan for the mother and each month has different pattern of herbal and dairy supplements to fulfill needs of growing fetus.

Prenatal Yoga and Meditation: Advocate for the adoption of prenatal yoga and meditation practices to guarantee the mother's physical and emotional well-being.

Education and Training: Organize educational workshops for pregnant women, providing guidance on Ayurvedic nutrition and lifestyle practices to promote a healthy pregnancy.

Postnatal Care:

Postpartum Nutrition: Recommend a diet including of readily digested foods such as khichdi, soups, and herbal teas to facilitate recuperation and promote lactation. *Sutikaparicharya* can be followed for better health of the mother.

Ayurvedic Postpartum Therapies: Implement *Abhyanga* (oil massages) and other Ayurvedic therapies to facilitate recuperation and alleviate postpartum depression.

Herbal Supplements for New Mothers: Offer Ayurvedic tonics and supplements such as *Dashamoola* and *Bala* to aid in postpartum recuperation and enhance lactation. Care for Infants (Ages 0-6 Months).

Breastfeeding Support: Encourage the practice of exclusively breastfeeding for the initial six months, with the aid of Ayurvedic techniques to improve the quality and quantity of breast milk. *Shatavari churna* should be used to enhance lactation. In non-availability of breast milk, milk from *Dhatri* should be taken.

Maternal Nutrition: It is important for the mother to consume a nourishing and well-balanced diet that includes Ayurvedic foods. This will help in the baby's development through breast milk. Childcare for Toddlers (Ages 6 Months - 3 Years).

Introduction of Solid Foods: Gradually incorporate semi-solid foods made using Ayurvedic principles, such as rice porridge, pureed fruits, and vegetables. *Acharya Kashyapa* prescribed to give Anna (solid food) in 10th month of life.

Nutrient-Rich Foods: Incorporate Ayurvedic foods that are high in nutrients, such as ragi (finger millet), ghee, and seasonal fruits, to promote healthy growth and development.

Natural drinks and Decoctions: Give moderate herbal teas such as fennel or cumin water to improve digestion and enhance immunity.

Establishing Regularity and Discipline: Implement consistent meal schedules and routines based on Ayurvedic principles to foster healthy eating habits and optimize digestion.

Monitoring Growth and Development: Consistently observe and evaluate the progress and nutritional condition of toddlers, administering

supplementary Ayurvedic supplements as necessary.

Parental Education: Provide parents with information about the significance of adopting an Ayurvedic lifestyle for their children's overall well-being, with a specific emphasis on dietary choices, sleep patterns, and daily routines Integrated Approach.

Partnership with Healthcare Providers: Provide comprehensive training to Anganwadi workers and healthcare personnel in Ayurvedic practices to enhance their ability to provide knowledgeable guidance and assistance.

Holistic Health Camps: Arrange camps that offer comprehensive Ayurvedic health evaluations, dietary guidance, and botanical supplements for expectant mothers and young individuals.

Community Outreach Programs: Conduct awareness campaigns and seminars to educate communities about the advantages of Ayurvedic nutrition and lifestyle practices from pregnancy to early childhood.

CONCLUSION: Incorporating Ayurvedic concepts into current government nutrition programs may provide a comprehensive method for tackling malnutrition in India. Ayurveda places great importance on maintaining a harmonious diet, ensuring efficient digestion, and adopting lifestyle habits that contribute to general well-being.

By integrating Ayurvedic dietary principles, herbal supplements, and therapies into initiatives such as POSHAN Abhiyaan and Pradhan Mantri Matru Vandana Yojana (PMMVY), the nutritional and health results for mothers, children, and adolescents can be greatly enhanced. This collaboration will address current dietary requirements and promote long-term health and well-being, ultimately contributing to the country's progress.

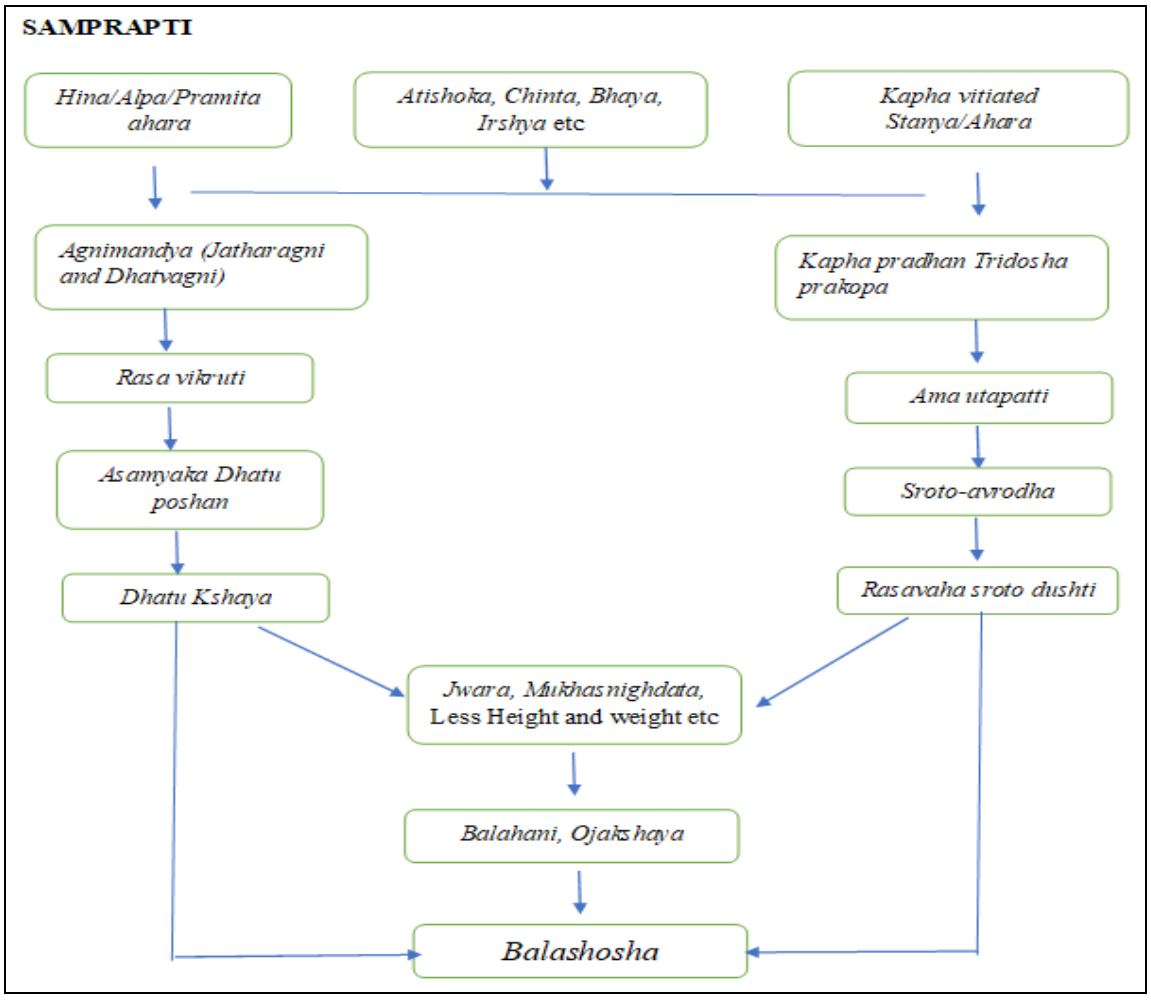

FIG. 1: PROBABLE SAMPRAPTI OF MALNUTRITION

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