Various Therapeutic Activities and Drug Delivery Strategies of Anethole: An Overview

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Abstract-
Background: Anethole is an organic compound with molecular formula $C_{10}H_{12}O$. Anethole is obtained from star anise, fennel and aniseed. Anethole exist as essential oil soluble in ethanol and partially soluble in water. Anethole is used in common treatment for many illnesses these days. Among its many medicinal properties include anti-inflammatory, anti-bacterial, anti-fungal, and anti-cancer properties. Since anethole is only partially soluble in water, it is integrated and delivered to the targeted organ by a variety of drug delivery methods to maximize therapeutic benefits. Different drug delivery systems consist of invasomes, liposomes, transdermal self-nano emulsifying systems, and more. These days, anethole is a commonly used with maximal benefits and minimal negative effects.
Objective: This review provides a brief information regarding anethole, its therapeutic activities, various extraction methods and drug delivery strategies.

Keywords: **Anethole, Therapeutic activity, Drug delivery, Extraction.**

1. INTRODUCTION

During ancient era, herbal source was used medicine for variety of diseases and disorders. But later this ratio decreased and allopathic medicine gained immense growth in field of medicine. During the Covid-19 phase worldwide herbal medicines were used to prevent the disease. The most significant component of star anise is Anethole, which is utilized in the food, flavoring, pharmaceutical, and perfume industries.[1] The monoterpene isomer of anethole (1-methoxy-1-propenyl-4-benzene) is primarily present in the essential oil of star anise (*Illicium verum Hook*. Family-llliciaceae), sweet anise/ fennel *(Foeniculum vulgare Mill* Family- Apiaceae), and anise (*Pimpinella anisum L*. Family- Apiaceae). Due to the presence of double bond in anethole molecule, it can exist as cis-isomer and trans-isomer. Trans-anethole is found to have a wide range of therapeutic activities like anti-cancer, anti-oxidant, anti-inflammatory, anti-microbial, etc. [2][3]. Anethole also possesses wide range of pharmacological actions such as anti-fertility, anti-fungal, anti-diabetic and so on.[4] Anethole, also known as 1-methoxy-4-(1-propenyl)benzene, is a natural flavor that is frequently used to mask disagreeable smells and sweeten baked goods, candies, ice creams, chewing gum, and especially some alcoholic beverages.[4][5] Many plants that grow in the Eastern Mediterranean Region, West Asia, the Middle East, Mexico, Egypt, and Spain have essential oils that contain anethole, including fennel, anise, and other members of the Apiaceae family as well as star anise.[4]

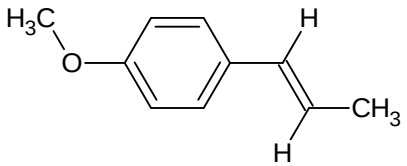

Fig 1: Structure of Trans- Anethole

Anethole can be obtained from 3 main sources namely, Star Anise (SA), Fennel and Aniseed. SA is *Illicium verum's* ripe dried fruit. Six to eight one-seeded, boat-shaped, woody, wrinkled, ridged, reddish-brown follicles make up its whorl, and their interior structure is smooth, glossy, and light brown in texture.[6][7] Anethole found about 85-90% in star anise.[6][8]
Typically, a perennial aromatic plant, *Foeniculum vulga*re is a member of the Apiaceae (Umbelliferae) family. The fruits are aromatic, ridged, and oblong or ellipsoid in shape.[9][10] 65. 05% trans-anethole was present in fennel fruit. Anise and fennel was found have been effective anti-feedants and indicating potential for gypsy moth controlled.[11]
Pimpinella anisum L., commonly known as anise, is indeed an annual herb with white flowers and small green to yellow seeds. It is cultivated in the Mediterranean region, India, and various other warm regions globally. The main purpose of

growing *Pimpinella anisum L*. is for its fruits, or seeds.[12] Trans-anethole content in anise oil ranges from 75% to 90%.[13]

2. EXTRACTION

Table 1: Extraction methods of Anethole

SOURCE	METHOD OF EXTRACTION	YEILD	REFERENCE
Fennel seeds	CO2 extraction	9.33%	[14]
Fennel powder	Steam distillation	2.95%	[15]
Fennel powder	Maceration	7.1-15.3%	[16][17]
Fennel fruit	Soxhlet	20.8%	[18]

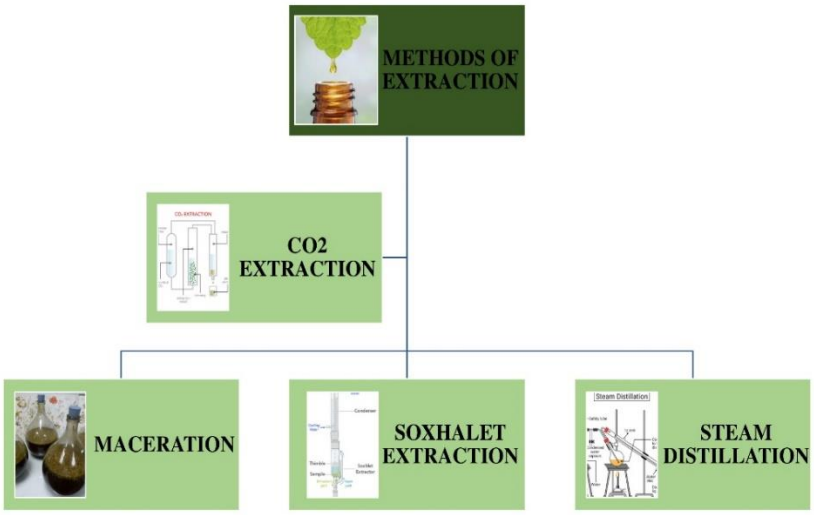

Fig.2: Extraction methods of anethole

Anethole can be extracted by following methods:

2.1. CO_2 Extraction

Bodsgard et al. used fennel seeds (around 1.4 g) sealed in a tea bag and placed in a 15 mL centrifuge tube with crushed dry ice. The tube is tightly capped, immersed in hot tap water (50−60 °C), causing CO_2 to form, submerging the pouch for anethole extraction. After boiling off, anethole coats the tube bottom. The process is repeated, and the tube is labeled and stored in a 0 °C freezer. 9.33% of the anethole was recovered from fennel seeds using CO_2 extraction.[14]

2.2. Steam distillation

N. Marčac et al. used fennel powder subjected to steam distillation used various solvents liked chloroform, petroleum ether, dichloromethane Further petroleum ether is evaporated and residue is weighed. Residue is stored at 4°C. 2.95 % anethole is obtained after steam distillation. [15]

2.3. Maceration

P. Mehra et al used required quantity of fennel powder was weighed and placed in vessel containing alcohol. Mixture was allowed to rested for period of 7 days. Occasional stirring was performed in 7 days. Later the mixture was strained.[16]

7.1-15.3% yield extract range of trans-anethole by using maceration.[17]

2.4. Soxhlet Extraction

F. A. S. Miranda used fennel fruits are ground and approximately weigh. Soxhlet apparatus is operated for interval of 6 hours. Solvents employed are ethanol 96%, n hexane, diethyl ether. Temperature is maintained for different solvents (Ethanol - 79°C, n hexane - 69°C, diethyl ether- 35°C). Residue is collected and purified using column chromatography (solvents- toluene (9): ethyl acetate (1) Using Soxhlet extraction, 20.8% of the anethole was extracted from the fennel fruits.[18]

3. THERAPEUTIC ACTIVITIES OF ANETHOLE

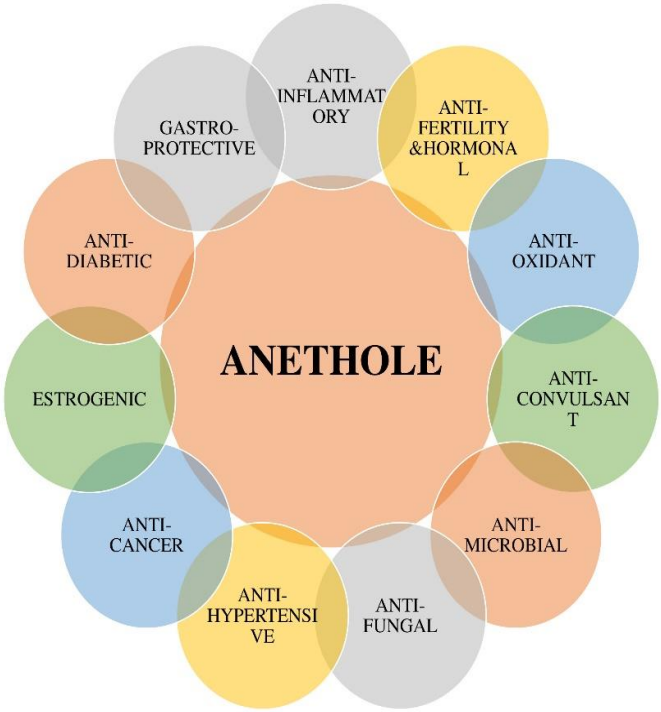

Fig.3: Therapeutic activities of Anethole

3.1. Anti-inflammatory

Inflammation is a response provided by immune system against infection and tissue injury. The molecular mechanism of inflammation involves the recognition of specific molecular patterns associated with infection or tissue injury. This recognition triggers a complex process mediated by key regulators, leading to the selective expression of proinflammatory molecules. The steps typically include vasodilation, increased permeability, recruitment of immune cells, and the release of signaling molecules like cytokines. Prolonged inflammation, often caused by persistent inducers or genetic variations, can lead to various inflammatory diseases and adverse health effects.[19]

The inflammation serves as a crucial defense mechanism while also being implicated in various diseases. They intricate interplay of immune cells, cytokines, and signaling pathways underscores its complexity. The dual nature of inflammatory responses underscores the delicate balance required for maintaining health.[20]

Chung K et al. observed that chronic obstructive pulmonary disease (COPD) posed significant threats to public health and will continue to do so. Globally, COPD treatment is becoming worsened to healthcare systems due to its high rate of occurrence, morbidity and mortality.[21] COPD found to be greatest in patients who smoked 20 cigarettes or more a day (20% and 18.5% respectively in men and women).[22] Sputum has been found to contain elevated levels of interleukins,(IL-6, IL-1β, IL-8); these levels have been found to rise further during exacerbations, and the bronchiolar epithelium overexpresses MCP-1 and IL-8. LTB4 and IL-8 can explain sputum's neutrophil chemotactic activity.[23]

Kim et.al. demonstrated that by lowering the concentrations of proinflammatory cytokines like Tumour Necrosis Factor (TNF-a) and IL-6, trans-anethole reduced chronic inflammation in a mouse model of COPD, including cytotoxicity, increase in proinflammatory cells, and lung damage caused by porcine pancreatic elastase (PPE) and Lipopolysaccharide (LPS). Airspace enlargement and alveolar destruction were observed in lung histopathology. Moreover, trans-anethole dramatically reduced the elevated blood pressure linked to persistent inflammation.[24]

3.2. Gastro protective activity

Ethanol is consumed by population on a very enormous scale. Ethanol causes the erosion of mucosal layer which protects the stomach lining. The administration of ethanol decreases the secretion of bicarbonate, gastric mucus, and nitric oxide and results in gastric necrotic damage and subsequently causes inflammatory cell infiltration. Furthermore, ethanol decreases the amount of blood flowing through the stomach and causes oxidative stress by raising the synthesis of malondialdehyde and lowering that of glutathione.[25]

Ethanol increases the risk of gastric ulcers by eroding the gastric mucosal layer. Anethole provides gastro protective action against ethanol. Pretreatment utilizing anethole reduces the risk of erosion mucosal layer. Anethole is widely used to protect erosion not gastric lesions. [4][26]

Coelho-de-souza et al. studied on *Croton Zehntneri*, a plant from northeastern brazil, was used in folk medicine for gastrointestinal issues. Its essential oil (EOCZ- essential oils of *Croton Zehnteri*) and main component anethole showed dose-dependent gastroprotection against ethanol- and indomethacin-induced gastric damage in mice and rats. Both

substances increased mucus production in gastric mucosa in ethanol-induced ulcer models, suggesting a gastroprotective potential. However, they had no significant impact on stress-induced ulcers or pylorus-ligated model parameters, indicating specificity in their effects. This study suggests that, EOCZ, particularly anethole, can be a therapeutic option for gastric ulcer treatment.[27]

3.3.Anti diabetic

Diabetes mellitus (DM) is a common metabolic/endocrine disorder throughout the world and cause serious medical problems to human health.[28]

R. stefanescu et. al. studied demonstrated that fennel essential oil had antihyperglycemic effects in rats with diabetes induced by streptozotocin. Initially the fennel essential oil subjected to Gas Chromatography- Mass Spectrometry (GC-MS) and its components were determined. Trans anethole and fenchone were found to be the major components. This essential oil were subjected to in-vivo study on rats for 4 weeks via oral as well as topical route of administration. It was observed that, the blood glucose levels reduced regardless of the route of administration. Hence, an anti-diabetic effect was observed[29].

Samadi-Noshahr et al. observed that significant global health challenge posed by diabetes mellitus and its impact on diabetic nephropathy (DN). It was found that, when Streptozotocin induced Diabetic rats were treated with trans-anethole there was a drastic decrease in the fasting blood glucose levels. The use of trans-Anethole (TA), a compound found in essential oils, alone or in combination with losartan, protects against STZ- induced kidney injury in diabetic conditions.[30] Anethole shows promising anti-diabetic effects by acting on ion channels .[31]

3.4.Estrogenic activity

Despite variations in its quantity, tropism, tissue-specific distribution, and receptor affinity throughout life, estrogen is an essential enzyme for both genders' survival and health. Beyond being a sex hormone that induces estrus, estrogen is more. In actuality, practically every element of male and female health is regulated by this steroid hormone.[32].

Trans-anethole is widely used in developing secondary female characteristics. Trans anethole when administered to immature female rats results in high estrogenic activity.[4] [33]

Albert-puleo et al. discovered plant anise had been used as an estrogen alternative for thousands of years. It was specifically said to enhance milk secretion, facilitate menstruation, eased childbirth, lessen climacteric symptoms in males, and boost libido. Anethole, the primary component of anise essential oils, had long been thought have been the potent estrogenic agent.[34]

3.5. Anti-cancer

One of the prime causes of death worldwide is cancer. A sequence of progressively occurring gene mutations that alter cell activities causes cancer. Such gene mutation cause abnormal cell proliferation. [35] However, Jemal et al. studied that factors including population aging and expansion, as well as increasing number of people adopting cancer related lifestyle choices like smoking, inactivity and westernized lifestyles the incidence of cancer is rising in economically developing nations. [36]

According to Contant et al., apoptosis, autophagy, and oxidative stress are among the mechanisms by which the anethole treatment specifically promotes anti-oral cancer properties. It also modifies proliferative signaling pathways. As a natural chemical phytoconstituent with potent therapeutic action, anethole shows considerable promise for its potential use in the treatment of gum cancer. The impact of anethole on proteins involved in pro-carcinogenic and apoptotic signaling pathways which was evaluated by using immunoblotting. Anethole demonstrated the capacity to increase intracellular glutathione (GSH) activity, decrease the generation of reactive oxygen species (ROS), and induce autophagy. The administration of anethole treatment results in the suppression of oncogenes (cyclin D1) and the upregulation of cyclin-dependent kinase inhibitor (p21WAF1). Additionally, it elevates the expression of the p53 gene while suppressing the markers associated with the epithelial-mesenchymal transition. Anethole can be a promising molecule for the treatment of oral cancer, according to these findings.[37]

Anethole shows promised as an anticarcinogenic and chemo preventive agent. Its influence on immunomodulatory actions may benefit overall immune function. Moreover, anethole exhibits neuroprotective qualities, implying potential applications in conditions related to neurological health [31]

3.6. Diuretic

Diuretics are a versatile and invaluable class of drugs that are frequently used to treat electrolyte imbalances, heart failure, and hypertension. Diuretics are a broad class of medications that are still very useful in treating hypertension and hypervolemic conditions. [38]

Tufer et al. performed the in-vivo studies of 80 % methanolic extracts of *Croton macrostachyus* on rats loaded with saline. The level of diuresis of methanolic extract on saline loaded rats were compared with its aqueous extract. However, the methanolic extract showed a long duration of anti-diuretic activity than that of the aqueous extract. [39]

3.7. Anti-fungal

A range of severity levels of superficial, cutaneous, subcutaneous, mucosal, and systemic infections can be caused by fungi. Human microbiota includes organisms like *Candida spp.* that can cause invasive candidiasis, a potentially fatal

infection that can occur in immune compromised patients like HIV patients, cancer patients undergoing chemotherapy, and patients taking immunosuppressive drugs.[40]

Huang et al. found that inhibitory activity against plant pathogenic fungi exhibited by the fruit essential oil of I. verum and trans-anethole. The oil's high trans-anethole content which was found to be the primary active ingredient among its volatile constituents, is responsible for its antifungal activity. It is possible to develop fruit essential oil and trans-anethole from *I. verum* as natural fungicides, or fumigants, for the control of plant diseases in the preservation of fruits and vegetables.[41]

3.8. Anti-microbial

Indeed, the excretion of proteases by bacteria and fungi during infections can lead to diverse pathogenic outcomes, including pain, edema, shock, and the translocation of bacteria into systemic circulation, ultimately causing septicemia. These enzymes play a crucial role in the virulence of microbial pathogens. [42]

Foroughi et al. found that the essential oil of *Foeniculum vulgare* showed anti-bacterial activity against *Escherichia coli* and *Staphylococcus aureus*. This activity was determined by performing the anti-microbial assay of the oil by well diffusion method. Such an activity was due to the presence of the major phytochemical named trans-anethole[43].

3.9. Anti-convulsant

The medical term for recurrent, spontaneous seizures is "epilepsy." There are many causes of epilepsy, and all of them point to underlying brain dysfunction. One of the most prevalent neurologic disorders is epilepsy, which affects about 50 new cases out of every 100,000 people annually.[44]

Guedes et al. found that Trans-Anethole has promising activity as an antiseizure agent in encephalographic and behavioral research. The most effective dose of TAN (trans-anethole) 400 mg/kg, was found in study and is able to shorten the duration of tonic seizures in MES (maximal electric shock) and tonic-clonic seizures in mice with PTZ (pentylenetetrazole)-induced models. Additionally, by delaying the onset of the first myoclonic jerk and tonic-clonic seizure, this dose prevents animals from dying during the PTZ test (pentylenetetrazole).[45]

3.10. Anti-oxidant

By preventing oxidation processes, antioxidants are essential for food preservation. They are also a key component of many dietary supplements, nutraceuticals, and functional food ingredients that promote health.[46]

Galicka et al. found that trans-anethole is a non-toxic substance which shows protective properties against hydrogen peroxide-induced toxicity, considering hydrogen peroxide is a reactive oxygen species generated during normal cellular metabolism. This suggests potential benefits in managing oxidative stress. When the cells were treated with hydrogen peroxide it led to alterations in the type I collagen mRNA expressions. Hence, the amount of collagen synthesized was reduced. But when the cells were pretreated with trans-anethole such an alteration was prevented. Hence, trans-anethole was found to have an anti-oxidant activity against the strong oxidizing agent, hydrogen peroxide[47].

3.11. Anti-fertility

Numerous medicinal plant extracts have been investigated for their ability to prevent infertility in both male and female subjects. Biologically active botanical compounds or environmentally friendly plant-based fertilizer regulators are required.[48]

Dhar et al. observed that trans-anethole appears to be operating at two stages: the first is the attachment, often referred to as "attachment," between the blastocyst and the uterus, which determines the blastocyst's final position in relation to the uterus; the second is the actual trophoblast cell penetration into the nidus, also known as the "trophoblastic invasion." The primary hormonal agents that inhibit the process of implantation are progesterone and estrogen. Since trans-anethole exhibited strong estrogenic activity, a disruption in the ideal ratio of the two hormones' "balance" could be the cause of the anti-implantation activity that was seen. The findings show that trans-anethole has neither progestational nor anti-progestational effects at the dosage used. The progesterone component of the "balance" is not affected by the chemical. The comparatively higher dominance of the estrogen factor is the cause of the anti-implantation activity. Such an anti-implantation activity was found in the in-vivo studies on immature female rats using trans-anethole at a dose of 80 mg/kg. Additionally, trans-anethole has demonstrated a strong early abortifacient effect in rats. [33]

Table 2: Therapeutic activities of anethole summary

Sr. no	Anethole or its derivatives	Therapeutic activity	Mechanism	References
1	Trans-anethole	Anti-inflammatory	Lower down the concentration of pro-inflammatory mediators (Tumour Necrosis Factor -a and Interleukin-6)	[24]
2	Trans-anethole and *Croton Zehntneri*	Gastro-protective	Shows increased production of gastric mucosa	[27]

3	Anethole	Anti-diabetic	Inhibiting tyrosine-protein phosphatase non-receptor type 1 (PTP1B)	[29]
4	Trans-anethole	Estrogenic	-	[34]
5	Anethole	Anti-cancer	Supressess oncogenes (cyclin D1) and the upregulation of cyclin-dependent kinase inhibitor (p21WAF1	[37]
6	Methanolic extract of anethole (80%)	Diuretic	-	[39]
7	Trans-anethole	Anti-fungal	Inhibits the growth of fungus (*Cladosporium fulvium*, *Fusarium tricinctum*,)	[41]
8	Trans-anethole	Anti-microbial	-	[43]
9	Trans-anethole	Anti-covulsant	Trans-anethole 400mg/kg reduces risk of seizures in PTZ (pentylenetetrazole)-induced models	[45]
10	Trans-anethole	Anti-oxidant	Protective properties against hydrogen peroxide-induced toxicity	[47]
11	Trans-anethole	Anti-fertility and hormonal activity	Inhibits the process of implantation	[33]

4. VARIOUS DRUG DELIVERY STRATEGIES OF ANETHOLE

Drug delivery involves various methods to administer pharmaceutical compounds for therapeutic effects in humans or animals. It can include oral tablets, injections, patches, and other delivery systems. Nasal and pulmonary drug delivery offer viable alternatives to traditional parenteral methods, especially for peptides and proteins. These routes can enhance patient compliance and provide effective therapeutic outcomes. The advancement in drug delivery systems continues to contribute to the evolution of medical treatments. [49]

Advancements in drug delivery systems have indeed focused on enhancing solubility, stability, pharmacological activity, and minimizing side effects, contributing to significant progress since the 1950s. However, nanoparticles offer promising advantages in drug delivery. Their small size allows for targeted drug delivery, improving drug bioavailability and minimizing side effects. Liposomes, in particular, can enhance drug stability, increase circulation time, and facilitate controlled release, contributing to improved therapeutic outcomes. The diverse range of nanoparticle carriers provides versatility in addressing specific drug delivery challenges.[50]

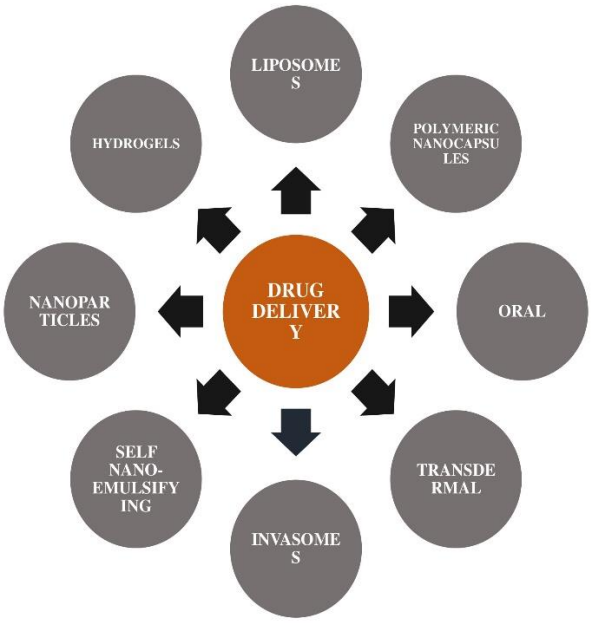

Fig.4: Drug delivery of anethole

4.1. Liposomes

Liposomes were discovered by Alec D. Bangham in the 1960s. Lipid vesicles are one or more lipid bilayers encapsulating an aqueous compartment. Due to their structural similarity to cellular membranes and the ability to incorporate diverse substances, liposomes are considered to be effective drug-carrier systems. They are primarily composed of phospholipids, which have hydrophilic heads and hydrophobic tails. [51]

Liposomes indeed exhibit a wide size range, from very small 0.025 µm to large 2.5 µm vesicles. They are classified into three categories- Multilamellar Vesicles (MLV), Large Unilamellar Vesicles (LUV), and Small Unilamellar Vesicles (SUV).[52]

Kfoury et al. concluded that the Cyclodextrins (CDs) indeed play a crucial role in pharmaceuticals, addressing challenges like drug solubility and stability. Their cyclic structure, comprising 6, 7, or 8 glucose units (α-, β-, and γ-cyclodextrin), enables effective drug encapsulation and improved bioavailability. CDs can form inclusion complexes with aromatic compounds, improving their stability, solubility, and bioavailability. This is particularly beneficial in various applications, including the enhancement of antimicrobial activity and reduction of volatility in aromas.[53]

The entrapment of hydrophobic drugs in liposomes' aqueous core as soluble inclusion complexes with cyclodextrins is a promising alternative to use organic solvents in pharmaceutical preparations. This leads to the formation of drug-in-cyclodextrin-in-liposome (DCL) systems, which can enhance drug solubility and stability, while also can prevent the rapid release of poorly aqueous soluble drugs incorporated in the lipid bilayer of conventional liposomes.[54]

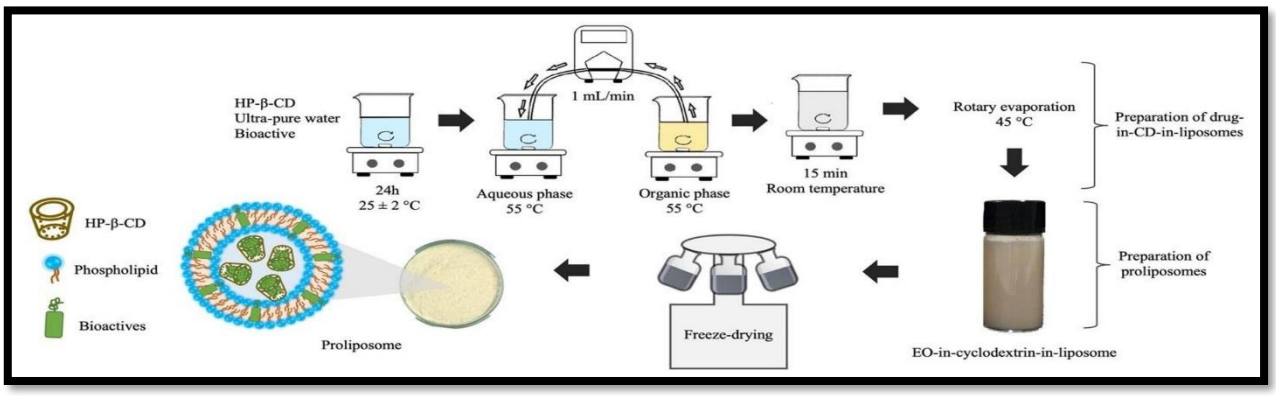

Fig.5: Liposomal Drug Delivery System of Anethole.

4.2. Oral drug delivery system

The oral method of drug administration is the most commonly used for both conventional and novel drug delivery. The reason for this preference is apparent due to its ease of administration and widespread acceptance by patients. [55]
Fei Han et al. had observed the oral bioavailability of Anethole trithione (ATT), which is poorly water-soluble and lipophilic. This was significantly overcome by lipid-based formulations. The drug's solubilization behavior was influenced by its lipid composition, while the formulation had an effect on the lipid digestion rate.[56]

4.3. Transdermal drug delivery system

The definition of transdermal drug delivery is self-contained, discrete dosage forms that deliver drugs through the skin when applied to the intact skin. [57] Transdermal Drug Delivery involves the penetration of drug via the skin followed by its entry into the systemic circulation. This type of drug is carried out with the help of transdermal patches. Such a drug-delivery strategy has certain advantages which include, bypassing of the first-pass metabolism, stability of drug concentration in the systemic circulation and avoiding gastric disturbances due to the drug. The formulation of transdermal patches involves the use of one of the main ingredients called penetration enhancers which helps in the penetration of drug into the skin.[58]
As per Krishnaiah et al. anethole played an effective role in enhancing the penetration of Selegiline Hydrochloride in the transdermal drug delivery. It was found that, the hydroxypropyl methylcellulose gel of selegiline hydrochloride (SH) which was containing the terpene, anethole increased the penetration of SH by 2.6 folds as compared to that devoid of anethole. Hence, anethole can be used as a penetration enhancer in transdermal patches[59]Valsartan, a medication that is extremely lipophilic, appears to be absorbed through the skin more readily when the enhancers are lipophilic. The terpene enhancer that improved valsartan penetration the greatest was anethole, followed by menthone. Anethole considerably increased the penetration of valsartan. [57]

4.4. Invasomes

A novel family of vesicles known as Invasomes is significantly enhancing active pharmaceutical drugs' transdermal penetration. These vesicles' structure includes phospholipids, ethanol, and different terpenes or combinations of terpenes. These components had outstanding transdermal penetration properties.[60]
As per Lakshmi et al. three distinct terpenes anethole, limonene, and fenchone as well as soya lecithin were used to encapsulate tolterodine tartrate, an excellent transdermal medication, into an invasome formulation.[61][62]

4.5. Nano-formulations:

4.5.1. SNEDDS (Self-nano emulsifying drug delivery system)

Because of its self-administration ability, patient compliance, and safety, oral administration is still the best method for delivering drugs. The multiple obstacles at the gastro-intestinal (GI) tract have restricted oral delivery, even though it is the most practical mode of administration. A combination of oils, surfactants, and co-surfactants or co-solvents has been referred to as SNEDDS. [63]
As per, Parmar et al. when gently shaken, hydrophilic co-solvents or co-emulsifiers are typically added to isotropic mixtures of drug, lipid, and surfactants called SNEDDS, which produce minuscule oil droplets in water nano emulsion.[64]. As per, Ren et al. when Tween 80 and Cremophor RH40 were used together, ATT (Anethole trithione) SNEDDS quickly created a nano-emulsion; the emulsification time was significantly reduced.

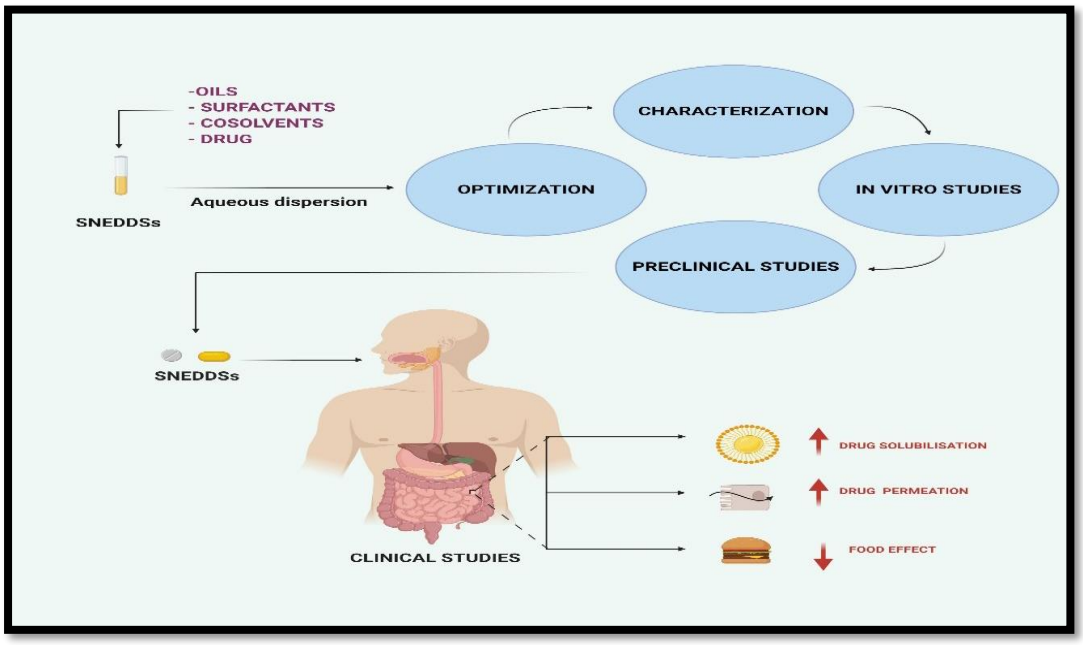

Fig.5: Overview of SNEDDS drug delivery system.

The rate of dissolution, solubility and ATT's stability was greatly improved. In contrast with ATT tablets, SNEDDS ATT was quickly distributed regardless of the fluid condition, resolved. In contrast to one surfactant or a mix of surfactants employed in. The SNEDDS may preferentially produce more surfactants partitioning to the water-oil interface.[65]

4.5.2. Nanoparticles

Nanoparticles are discrete atom assemblages at the 10–9 m nanoscale. As a result, their diameters lie between those of ions and macroscopic solids (10-10 m).[66]

Esfandyari-Manesh et al. performed evaporation of emulsification solvent and nanoprecipitation were used to create nanoparticles. In drug release studies, there was an initial burst release followed by a drug release in slow manner. Anethole and carvone are naturally occurring compounds with antibacterial properties found in many essential oils. Essential oil-loaded PLGA nanoparticles may be helpful in biomedical applications, according to antimicrobial research. It can be challenging to effectively entrap volatile essential oils using conventional techniques like emulsification and solvent evaporation. However, a successful method for creating volatile monoterpene-loaded PLGA nanoparticles was carried out. [67][68]

4.5.3. Polymeric Nanocapsules

Nanocapsules bear similarities to vesicular systems, wherein a drug is entrapped within a cavity made up of a polymeric membrane encircling an inner liquid core. The active ingredient can be present in nano-vesicular systems with a typical core-shell structure in liquid, solid, or molecular dispersion form. The drug is entrapped within a reservoir or cavity surrounded by a polymer membrane or coating cavity. Depending on the raw materials and preparation technique, this reservoir may be hydrophobic or lipophilic.[69]

As per Granata et al. trans-anethole chemotype (FEO) was efficiently encapsulated into polymer-based particles by the use of premade polymers' interfacial deposition technology. Using NMR studies, it was shown that FEO was encapsulated in polycaprolactone (PCL) polymer nanocapsules. The delivery of FEO by this green nanosystem may be appropriate, and it may also open the door to other uses in a number of industries, most notably the pharmaceutical one.[70]

4.6. Hydrogels gels

Since the early 1960s, hydrogels a novel drug delivery method have been investigated. Cross-linked hydroxyethyl methacrylate (HEMA) hydrogels were the first type of hydrophobic gel that Wichterle and Lim et al. created for biological purposes. There are two types of hydrogels: physically cross-linked or reversible hydrogels, which dissolve and break down during water absorption, and chemically cross-linked or permanent hydrogels, which are stable to degradation during swelling.[71][72][73]

As per Tas et al. common treatment for rheumatoid arthritis is etodolac, a highly lipophilic anti-inflammatory medication taken orally twice daily at a dose of 200 mg. Gastrointestinal disturbances are the most common side effect of etodolac therapy; these are typically mild and reversible, but in certain patients, peptic ulcers and severe gastrointestinal bleeding may occur. The topical administration of etodolac appears to be the best method for achieving high drug concentration at the application site while removing these side effects by formulating the same into Carboxymethyl cellulose Hydrogel. However, the introduction of anethole into the CMC hydrogel enhanced the penetration and absorption of Etodolac onto the skin.[74]

Table 3: Summary of drug delivery strategies of anethole

Sr No.	Drug/Combination	Matrix for Drug Delivery	Drug Delivery Type	Reference
1.	Valsartan	Transdermal patches	Transdermal	[75]
2.	Cyclodextrin	Liposomes	Targeted	[54]
3.	Anethole Trithione	Self-Nanoemulsifying	Oral	[65]
4.	Anethole and Carvone	PLGA	In-vitro	[67][68]
5.	Trans-anethole Chemotype	PCL	Oral	[70]
6.	Etodolac and anethole	CMC	Topical	[74]

5. CONCLUSION

Anethole is essential oil obtained from star anise, aniseed and fennel. The aforementioned review taught us about a number of pharmaceutical distribution methods as well as the therapeutic benefits of anethole. Because anethole is a phytoconstituent, the adverse effects are least. These days, herbal products are used all over the world to maximize

benefits and minimize negative adverse effects. Anethole is the current scientific trend used to treat a variety of illnesses including diabetes, cancer, epilepsy, inflammation and many others. Anethole has demonstrated amazing therapeutic benefits. This study offers comprehensive information about anethole that can be utilized as a research resource. Anethole is frequently used to demonstrate how drugs work in concert. Anethole can be formulated as novel formulation in treatment of various diseases.

Anethole was formulated into various formulations for various drug delivery routes like oral, transdermal, topical, etc. Such formulations could show a better effect at the target site than that of the conventional ones.

Hence, anethole having a wide range of activities can be delivered into the target site via variety of drug delivery strategies for treating a variety of disease with minimal adverse effects and minimal toxicity issues.

6. FUTURE PROSPECTIVE

When exposed to various elements like light, temperature, and oxygen, as well as interactions with other chemical components, anethole quickly broken down and degrade. Microcapsules serve as micro-reservoirs and can be used to "trap" anethole, providing superior protection. Emulsifying or dispersing the essential oils containing anethole in an aqueous solution of a wall material which also serves as an emulsifier is frequently the first step in the essential oil microencapsulation process. This occurs as a result of the EOs' liquid state at ambient temperature. Subsequently, it is imperative to dry the microcapsules under carefully regulated conditions to minimize the loss of encapsulated material due to volatilization. Since anethole is present essential oils obtained from sources like star anise, fennel and aniseed, it can be easily incorporated in microcapsules and delivered at targeted site via skin via topical drug delivery in form of cream. Also, another approach is incorporation of these microcapsules into transdermal patches.

REFERENCES:

[1] W. Sun, M. H. Shahrajabian, and Q. Cheng, " Anise (Pimpinella anisum L .), a dominant spice and traditional medicinal herb for both food and medicinal purposes ," *Cogent Biol.*, vol. 5, no. 1, p. 1673688, 2019, doi: 10.1080/23312025.2019.1673688.

[2] R. Ilijeva and G. Buchbauer, "Biological properties of some volatile phenylpropanoids," *Nat. Prod. Commun.*, vol. 11, no. 10, pp. 1619–1629, 2016, doi: 10.1177/1934578x1601101041.

[3] A. M. V. Ritter, F. Q. Ames, F. Otani, R. M. W. De Oliveira, R. K. N. Cuman, and C. A. Bersani-Amado, "Effects of anethole in nociception experimental models," *Evidence-based Complement. Altern. Med.*, vol. 2014, 2014, doi: 10.1155/2014/345829.

[4] B. Tavakkolifar, M. Massoudi, and J. Zarringhalam, "Review on pharmacological activities of Gum olibanum," *J. Med. Plants*, vol. 8, no. 32, pp. 14–19, 2009.

[5] P. Newberne *et al.*, "The FEMA GRAS assessment of trans-anethole used as a flavouring substance," *Food Chem. Toxicol.*, vol. 37, no. 7, pp. 789–811, 1999, doi: 10.1016/S0278-6915(99)00037-X.

[6] J. K. Patra *et al.*, "Star anise (Illicium verum): Chemical compounds, antiviral properties, and clinical relevance," *Phyther. Res.*, vol. 34, no. 6, pp. 1248–1267, 2020, doi: 10.1002/ptr.6614.

[7] Y. Zhang, H. Ji, and J. Yu, "Aromatic constituents and their changes of Illicium verum processed by different heating methods," *Ind. Crops Prod.*, vol. 118, pp. 362–366, 2018, doi: 10.1016/j.indcrop.2018.04.003.

[8] D. Chouksey, P. Sharma, and R. S. Pawar, "Biological activities and chemical constituents of Illicium verum hook fruits (Chinese star anise)," *Pelagia Res. Libr.*, vol. 1, no. 3, pp. 1–10, 2010, [Online]. Available: www.pelagiaresearchlibrary.com

[9] S. B. Badgujar, V. V. Patel, and A. H. Bandivdekar, "Foeniculum vulgare Mill: A review of its botany, phytochemistry, pharmacology, contemporary application, and toxicology," *Biomed Res. Int.*, vol. 2014, 2014, doi: 10.1155/2014/842674.

[10] F. D. Endalamaw and B. S. Chandravanshi, "Levels of major and trace elements in fennel (Foeniculum vulgari Mill.) fruits cultivated in Ethiopia," *Springerplus*, vol. 4, no. 1, pp. 1–10, 2015, doi: 10.1186/2193-1801-4-5.

[11] I. Kostić, J. Lazarević, D. Š. Jovanović, M. Kostić, T. Marković, and S. Milanović, "Potential of essential oils from anise, dill and fennel seeds for the gypsy moth control," *Plants*, vol. 10, no. 10, 2021, doi: 10.3390/plants10102194.

[12] S. Kadan, M. Rayan, and A. Rayan, "Anticancer activity of anise (Pimpinella anisum L.) seed extract," *Open Nutraceuticals J.*, vol. 6, no. 1, pp. 1–5, 2013, doi: 10.2174/1876396001306010001.

[13] D. M. El-Kersh *et al.*, "GC-MS metabolites profiling of anethole-rich oils by different extraction techniques: antioxidant, cytotoxicity and in-silico enzymes inhibitory insights," *J. Enzyme Inhib. Med. Chem.*, vol. 37, no. 1, pp. 1974–1986, 2022, doi: 10.1080/14756366.2022.2097445.

[14] B. R. Bodsgard, N. R. Lien, and Q. T. Waulters, "Liquid CO2 Extraction and NMR Characterization of Anethole from Fennel Seed: A General Chemistry Laboratory," *J. Chem. Educ.*, vol. 93, no. 2, pp. 397–400, 2016, doi: 10.1021/acs.jchemed.5b00689.

[15] N. Marčac *et al.*, "Hydrodistillation and Steam Distillation of Fennel Seeds Essential Oil: Parameter

Optimization and Application of Cryomilling Pretreatment," *Processes*, vol. 11, no. 8, 2023, doi: 10.3390/pr11082354.
[16] P. Mehra *et al.*, "Extraction of fennel oil using different methods and effect of solvent and time to maximize yield," *Int. J. Pharm. Pharm. Res.*, vol. 16, no. 1, pp. 59–66, 2019, [Online]. Available: www.ijppr.humanjournals.com
[17] J. Suksaeree, N. Chankana, C. Luprasong, and C. Monton, "Optimization of dynamic maceration of Clausena anisata (Willd.) Hook. f. ex Benth. leaves to maximize trans-anethole content," *SN Appl. Sci.*, vol. 3, no. 4, pp. 1–11, 2021, doi: 10.1007/s42452-021-04509-4.
[18] F. A. S. Miranda, "Continuous Essential Oil and Oleoresin Extraction from Star Anise (Illicium verum) by Hydrodistillation and Solvent Extraction," *Indones. Green Technol. J.*, vol. 11, no. 02, pp. 58–63, 2022, doi: 10.21776/ub.igtj.2022.011.02.03.
[19] A. U. Ahmed, "An overview of inflammation: Mechanism and consequences," *Front. Biol. China*, vol. 6, no. 4, pp. 274–281, 2011, doi: 10.1007/s11515-011-1123-9.
[20] M. R. Alonso, C. A. Anesini, and R. F. Martino, "Anti-inflammatory activity," *Sesquiterpene Lact. Adv. their Chem. Biol. Asp.*, pp. 325–346, 2018, doi: 10.1007/978-3-319-78274-4_14.
[21] J. B. Soriano and R. Rodríguez-Roisin, "Chronic obstructive pulmonary disease overview: Epidemiology, risk factors, and clinical presentation," *Proc. Am. Thorac. Soc.*, vol. 8, no. 4, pp. 363–367, 2011, doi: 10.1513/pats.201102-017RM.
[22] M. Cazzola, C. F. Donner, and N. A. Hanania, "One hundred years of chronic obstructive pulmonary disease (COPD)," *Respir. Med.*, vol. 101, no. 6, pp. 1049–1065, 2007, doi: 10.1016/j.rmed.2007.01.015.
[23] K. F. Chung, "Inflammatory mediators in chronic obstructive pulmonary disease," *Curr. Drug Targets Inflamm. Allergy*, vol. 4, no. 6, pp. 619–625, 2005, doi: 10.2174/156801005774912806.
[24] K. Y. Kim, H. S. Lee, and G. H. Seol, "Anti-inflammatory effects of trans-anethole in a mouse model of chronic obstructive pulmonary disease," *Biomed. Pharmacother.*, vol. 91, pp. 925–930, 2017, doi: 10.1016/j.biopha.2017.05.032.
[25] N. S. Karampour, A. Arzi, A. Rezaie, M. Pashmforoosh, and F. Kordi, "Gastroprotective effect of zingerone on ethanol-induced gastric ulcers in rats," *Med.*, vol. 55, no. 3, pp. 1–9, 2019, doi: 10.3390/medicina55030064.
[26] J. Malveira Cavalcanti *et al.*, "The essential oil of Croton zehntneri and trans-anethole improves cutaneous wound healing," *J. Ethnopharmacol.*, vol. 144, no. 2, pp. 240–247, 2012, doi: 10.1016/j.jep.2012.08.030.
[27] A. N. Coelho-de-Souza *et al.*, "Essential oil of Croton zehntneri and its major constituent anethole display gastroprotective effect by increasing the surface mucous layer," *Fundam. Clin. Pharmacol.*, vol. 27, no. 3, pp. 288–298, 2013, doi: 10.1111/j.1472-8206.2011.01021.x.
[28] P. Arulselvan, H. A. A. Ghofar, G. Karthivashan, M. F. A. Halim, M. S. A. Ghafar, and S. Fakurazi, "Antidiabetic therapeutics from natural source: A systematic review," *Biomed. Prev. Nutr.*, vol. 4, no. 4, pp. 607–617, 2014, doi: 10.1016/j.bionut.2014.07.009.
[29] R. Ștefănescu *et al.*, "Fennel Essential Oil as a Complementary Therapy in the Management of Diabetes," *Pharmaceutics*, vol. 15, no. 12, pp. 1–14, 2023, doi: 10.3390/pharmaceutics15122657.
[30] Z. Samadi-Noshahr *et al.*, "trans-Anethole attenuated renal injury and reduced expressions of angiotensin II receptor (AT1R) and TGF-β in streptozotocin-induced diabetic rats," *Biochimie*, vol. 185, pp. 117–127, 2021, doi: 10.1016/j.biochi.2021.03.011.
[31] A. C. Aprotosoaie, I. I. Costache, and A. Miron, "Anethole and its role in chronic diseases," *Adv. Exp. Med. Biol.*, vol. 929, pp. 247–267, 2016, doi: 10.1007/978-3-319-41342-6_11.
[32] S. Patel, A. Homaei, A. B. Raju, and B. R. Meher, "Estrogen: The necessary evil for human health, and ways to tame it," *Biomed. Pharmacother.*, vol. 102, no. October 2017, pp. 403–411, 2018, doi: 10.1016/j.biopha.2018.03.078.
[33] S. K. Dhar, "Anti-fertility activity and hormonal profile of trans-anethole in rats," *Indian J. Physiol. Pharmacol.*, vol. 39, no. 1, pp. 63–67, 1995.
[34] M. Albert-Puleo, "Fennel and anise as estrogenic agents," *J. Ethnopharmacol.*, vol. 2, no. 4, pp. 337–344, 1980, doi: 10.1016/S0378-8741(80)81015-4.
[35] S. H. Hassanpour and M. Dehghani, "Review of cancer from perspective of molecular," *J. Cancer Res. Pract.*, vol. 4, no. 4, pp. 127–129, 2017, doi: 10.1016/j.jcrpr.2017.07.001.
[36] A. Jemal, F. Bray, and J. Ferlay, "Global Cancer Statistics: 2011," *CA Cancer J Clin*, vol. 49, no. 2, p. 1,33-64, 1999, doi: 10.3322/caac.20107.Available.
[37] C. Contant, M. Rouabhia, L. Loubaki, F. Chandad, and A. Semlali, "Anethole induces anti-oral cancer activity by triggering apoptosis, autophagy and oxidative stress and by modulation of multiple signaling pathways," *Sci. Rep.*, vol. 11, no. 1, pp. 1–14, 2021, doi: 10.1038/s41598-021-92456-w.
[38] G. C. Roush, R. Kaur, and M. E. Ernst, "Diuretics: A review and update," *J. Cardiovasc. Pharmacol. Ther.*, vol. 19, no. 1, pp. 5–13, 2014, doi: 10.1177/1074248413497257.

[39] S. Tufer, E. Engidawork, A. G. Ayele, and C. Bashea, "Evaluation of the diuretic activity of aqueous and 80% methanol extracts of croton macrostachyus (Euphorbiaceae) leaves in saline-loaded rats," *J. Exp. Pharmacol.*, vol. 13, pp. 213–221, 2021, doi: 10.2147/JEP.S294062.
[40] G. K. K. Reddy, A. R. Padmavathi, and Y. V. Nancharaiah, "Fungal infections: Pathogenesis, antifungals and alternate treatment approaches," *Curr. Res. Microb. Sci.*, vol. 3, no. April, p. 100137, 2022, doi: 10.1016/j.crmicr.2022.100137.
[41] Y. Huang *et al.*, "Antifungal activity of the essential oil of illicium verum fruit and its main component trans-anethole," *Molecules*, vol. 15, no. 11, pp. 7558–7569, 2010, doi: 10.3390/molecules15117558.
[42] H. Maeda and T. Yamamoto, "Pathogenic mechanisms induced by microbial proteases in microbial infections," *Biol. Chem. Hoppe. Seyler.*, vol. 377, no. 4, pp. 217–226, 1996.
[43] A. Foroughi, P. Pournaghi, M. Zhaleh, A. Zangeneh, M. M. Zangeneh, and R. Moradi, "Antibacterial activity and phytochemical screening of essential oil of Foeniculum vulgare," *Int. J. Pharm. Clin. Res.*, vol. 8, no. 11, pp. 1505–1509, 2016.
[44] S. Weinstein, "Seizures and epilepsy: An overview," *Epilepsy Intersect. Neurosci. Biol. Math. Eng. Phys.*, pp. 65–77, 2016, doi: 10.1201/b10866-10.
[45] E. Da Guedes *et al.*, "Anticonvulsant Activity of trans -Anethole in Mice," *Biomed Res. Int.*, vol. 2022, 2022, doi: 10.1155/2022/9902905.
[46] F. Shahidi and Y. Zhong, "Measurement of antioxidant activity," *J. Funct. Foods*, vol. 18, pp. 757–781, 2015, doi: 10.1016/j.jff.2015.01.047.
[47] A. Galicka, R. Krętowski, J. Nazaruk, and M. Cechowska-Pasko, "Anethole prevents hydrogen peroxide-induced apoptosis and collagen metabolism alterations in human skin fibroblasts," *Mol. Cell. Biochem.*, vol. 394, no. 1–2, pp. 217–224, 2014, doi: 10.1007/s11010-014-2097-0.
[48] S. C. Joshi, A. Sharma, and M. Chaturvedi, "Antifertility potential of some medicinal plants in males: An overview," *Int. J. Pharm. Pharm. Sci.*, vol. 3, no. SUPPL. 5, pp. 204–217, 2011.
[49] G. Tiwari *et al.*, "Drug delivery systems: An updated review," *Int. J. Pharm. Investig.*, vol. 2, no. 1, p. 2, 2012, doi: 10.4103/2230-973x.96920.
[50] C. Li *et al.*, "Recent progress in drug delivery," *Acta Pharm. Sin. B*, vol. 9, no. 6, pp. 1145–1162, 2019, doi: 10.1016/j.apsb.2019.08.003.
[51] G. Bozzuto and A. Molinari, "Liposomes as nanomedical devices," *Int. J. Nanomedicine*, vol. 10, pp. 975–999, 2015, doi: 10.2147/IJN.S68861.
[52] A. Sharma and U. S. Sharma, "Liposomes in drug delivery: Progress and limitations," *Int. J. Pharm.*, vol. 154, no. 2, pp. 123–140, 1997, doi: 10.1016/S0378-5173(97)00135-X.
[53] M. Kfoury, L. Auezova, H. Greige-Gerges, S. Ruellan, and S. Fourmentin, "Cyclodextrin, an efficient tool for trans-anethole encapsulation: Chromatographic, spectroscopic, thermal and structural studies," *Food Chem.*, vol. 164, pp. 454–461, 2014, doi: 10.1016/j.foodchem.2014.05.052.
[54] R. Gharib, H. Greige-Gerges, A. Jraij, L. Auezova, and C. Charcosset, "Preparation of drug-in-cyclodextrin-in-liposomes at a large scale using a membrane contactor: Application to trans-anethole," *Carbohydr. Polym.*, vol. 154, pp. 276–286, 2016, doi: 10.1016/j.carbpol.2016.06.074.
[55] K. K. Jain, *Methods in Molecular Biology, Vol. 437: Drug Delivery Systems: Preface*, vol. 437. 2008.
[56] S. fei Han *et al.*, "Lipid-based formulations to enhance oral bioavailability of the poorly water-soluble drug anethol trithione: Effects of lipid composition and formulation," *Int. J. Pharm.*, vol. 379, no. 1–2, pp. 18–24, 2009, doi: 10.1016/j.ijpharm.2009.06.001.
[57] R. K. Subedi, S. Y. Oh, M. K. Chun, and H. K. Choi, "Recent advances in transdermal drug delivery," *Arch. Pharm. Res.*, vol. 33, no. 3, pp. 339–351, 2010, doi: 10.1007/s12272-010-0301-7.
[58] M. P. Wagh, H. Dalvi, and M. Bagal, "Formulation and evaluation of transdermal drug delivery system for simvastatin," *Indian Drugs*, vol. 46, no. 3, pp. 221–225, 2009, doi: 10.4103/jphi.JPHI.
[59] Y. S. R. Krishnaiah, S. M. Al-Saidan, and B. Jayaram, "Effect of nerodilol, carvone and anethole on the in vitro transdermal delivery of selegiline hydrochloride," *Pharmazie*, vol. 61, no. 1, pp. 46–53, 2006.
[60] O. S. Salih and E. J. Al-Akkam, "Review Article Invasomes as a Novel Delivery Carrier for Transdermal Delivery: Review Article Citation," *Medicon Pharm. Sci.*, vol. 2, no. 3, pp. 11–16, 2022.
[61] S. Jain, S. Tripathi, and P. K. Tripathi, "Invasomes: Potential vesicular systems for transdermal delivery of drug molecules," *J. Drug Deliv. Sci. Technol.*, vol. 61, p. 102166, 2021, doi: 10.1016/j.jddst.2020.102166.
[62] B. Kalpana and P. K. Lakshmi, "Transdermal permeation enhancement of tolterodine tartrate through invasomes and iontophoresis," *Der Pharm. Lett.*, vol. 5, no. 6, pp. 119–126, 2013.
[63] A. B. Buya, A. Beloqui, P. B. Memvanga, and V. Préat, "Self-nano-emulsifying drug-delivery systems: From the development to the current applications and challenges in oral drug delivery," *Pharmaceutics*, vol. 12, no. 12, pp. 1–52, 2020, doi: 10.3390/pharmaceutics12121194.
[64] K. Parmar, J. Patel, and N. Sheth, "Self nano-emulsifying drug delivery system for Embelin: Design,

characterization and in-vitro studies," *Asian J. Pharm. Sci.*, vol. 10, no. 5, pp. 396–404, 2015, doi: 10.1016/j.ajps.2015.04.006.

[65] F. Ren, Q. Jing, J. Cui, J. Chen, and Y. Shen, "Self-Nanoemulsifying drug delivery system (SNEDDS) of anethole trithione by combined use of surfactants," *J. Dispers. Sci. Technol.*, vol. 30, no. 5, pp. 664–670, 2009, doi: 10.1080/01932690802598960.

[66] J. F. Banfield and H. Zhang, "Nanoparticles in the environment," *Rev. Mineral. Geochemistry*, vol. 44, pp. 1–58, 2001, doi: 10.2138/rmg.2001.44.01.

[67] A. Blanco-Padilla, K. M. Soto, M. Hernández Iturriaga, and S. Mendoza, "Food antimicrobials nanocarriers," *Sci. World J.*, vol. 2014, 2014, doi: 10.1155/2014/837215.

[68] M. Esfandyari-Manesh *et al.*, "Study of antimicrobial activity of anethole and carvone loaded PLGA nanoparticles," *J. Pharm. Res.*, vol. 7, no. 4, pp. 290–295, 2013, doi: 10.1016/j.jopr.2013.04.019.

[69] C. E. Mora-Huertas, H. Fessi, and A. Elaissari, "Polymer-based nanocapsules for drug delivery," *Int. J. Pharm.*, vol. 385, no. 1–2, pp. 113–142, 2010, doi: 10.1016/j.ijpharm.2009.10.018.

[70] G. Granata, C. Riccobene, E. Napoli, and C. Geraci, "Polymeric Nanocapsules Containing Fennel Essential Oil: Their Preparation, Physicochemical Characterization, Stability over Time and in Simulated Gastrointestinal Conditions," *Pharmaceutics*, vol. 14, no. 4, 2022, doi: 10.3390/pharmaceutics14040873.

[71] P. Ghasemiyeh and S. Mohammadi-Samani, "Hydrogels as Drug Delivery Systems; Pros and Cons," *Trends Pharm. Sci.*, vol. 5, no. 1, pp. 7–24, 2019, doi: 10.30476/TIPS.2019.81604.1002.

[72] Q. Chai, Y. Jiao, and X. Yu, "Hydrogels for biomedical applications: Their characteristics and the mechanisms behind them," *Gels*, vol. 3, no. 1, 2017, doi: 10.3390/gels3010006.

[73] M. Hamidi, A. Azadi, and P. Rafiei, "Hydrogel nanoparticles in drug delivery," *Adv. Drug Deliv. Rev.*, vol. 60, no. 15, pp. 1638–1649, 2008, doi: 10.1016/j.addr.2008.08.002.

[74] C. Tas, Y. Ozkan, A. Okyar, and A. Savaser, "In vitro and ex vivo permeation studies of etodolac from hydrophilic gels and effect of terpenes as enhancers," *Drug Deliv.*, vol. 14, no. 7, pp. 453–459, 2007, doi: 10.1080/10717540701603746.

[75] A. Ahad, M. Aqil, and A. Ali, "The application of anethole, menthone, and eugenol in transdermal penetration of valsartan: Enhancement and mechanistic investigation," *Pharm. Biol.*, vol. 54, no. 6, pp. 1042–1051, 2016, doi: 10.3109/13880209.2015.1100639.