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Exploring the potential of fennel and its chief constituent anethole as therapeutic agents for endometriosis: A review of current evidence and mechanistic insights

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Abstract
Background: Ectopic endometrial tissue, inflammation, oxidative stress, angiogenesis, and pain are the hallmarks of endometriosis, a chronic, estrogen-dependent illness. The need for new adjunctive medications is highlighted by the fact that traditional treatments, such as hormone suppression and surgery, are frequently ineffective or poorly tolerated. The anti-inflammatory, antioxidant, antispasmodic, and phytoestrogenic qualities of fennel (*Foeniculum vulgare*) and its main phenylpropene component, anethole, may target important endometriosis triggers.
Methods: With a focus on molecular pathways pertinent to endometriosis, we conducted a thorough literature analysis of *in vitro*, *in vivo*, and clinical research investigating fennel extracts or pure anethole. PubMed, Scopus, and ScienceDirect were among the databases that were examined; they included foundational work and research conducted during the last ten years.
Findings: Immunomodulatory and anti-inflammatory effects: In preclinical models, anethole increases IL-10, decreases pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), inhibits NF-κB activation, and suppresses COX-2-mediated prostaglandin formation.
Antioxidant activity: Anethole and fennel extracts increase endogenous antioxidant enzymes (SOD, CAT, GPx), reduce lipid peroxidation (MDA), and reduce the production of reactive oxygen species.
Anti-invasive and anti-angiogenic properties: Anethole inhibits the expression of MMP-2/9 and VEGF/VEGFR-2 signalling, which may hinder lesion invasion and neovascularization.
Hormonal modulation: Although its overall impact on endometriosis is yet unknown, anethole, a weak phytoestrogen, relaxes the smooth muscles of the uterus and may affect the balance of estrogen and progesterone.
Clinical data: Research on primary dysmenorrhea shows that fennel oil, which is high in anethole, offers analgesia on par with NSAIDs. However, there are currently no clinical research evaluating the effects of fennel or anethole on endometriosis.
Conclusion and Prospects for the Future: Fennel and anethole are multi-targeted modulators of pathways related to endometriosis, according to preclinical research. However, there are still important limitations in pharmacokinetic characterisation, direct assessment in endometriosis models, and standardized formulations. To determine safety, ideal dosage, and therapeutic effectiveness in endometriosis-affected women, well-planned, placebo-controlled clinical studies utilizing pure anethole or defined fennel extracts are required.

Keywords: Endometriosis, fennel (*Foeniculum vulgare*), anethole

Introduction
The World Endometriosis Society defines endometriosis as an inflammatory disease that manifests as endometrium-like tissue outside of the uterus. Ten percent of women who are of reproductive age and thirty to fifty percent of women who experience pelvic pain or infertility have endometriosis. When the endometriotic tissue extends 5 mm or more into the retroperitoneal area, it is categorized as either superficial or deeply infiltrating endometriosis (DIE). The uterus (adenomyosis), ovary (endometrioma), pelvic peritoneum, bladder/ureter, rectum, colon, uterosacral ligaments, rectovaginal septum, vaginal wall, pouch of Douglas, and other places in the pelvis can all exhibit endometriosis. Distant regions such the lungs, liver, pancreas, surgical scars, inguinal area, and even the brain are more uncommon places for endometriotic implants, and as a result, the symptoms that present vary.

Regarding the degree and severity of endometriosis, there are various classification schemes. As of right now, the updated American Society for Reproductive Medicine score is the most extensively utilized globally (stage I, mild; stage II, moderate; stage III, moderate; and stage IV, severe). This score does not account for the profoundly infiltrating endometriotic lesions, despite being reasonably simple to use. The ENZIAN classification, which offers a morphologically descriptive description of DIE, was created as a result. Endometriosis can manifest clinically as severe dysmenorrhea (difficult periods), dyspareunia (painful intercourse), or persistent pelvic pain, in addition to asymptomatic and unexplained infertility. There may be other, more specific symptoms depending on the site of infection (e.g. dysuria by bladder infection) [1].

Up to 43% of women suffer from sexual dysfunction, which is incredibly prevalent in the general community. Sexual dysfunction may be much more common in women with chronic illnesses, particularly if those conditions include recurrent or chronic pain. Desire, arousal/lubrication, and orgasm/sexual satisfaction are the three stages of the physiological female sexual response.

Hypoactive sexual desire disorder (16-32%), sexual arousal disorder (7-48%), painful sexual disorder/dyspareunia (1-45%), and orgasmic disorder (5-42%) are the most prevalent sexual disorders among women. Research on the sexual function of women with chronic illnesses has shown that these conditions can impact several aspects of the sexual response. Nonetheless, some research has been done to assess sexual function in endometriosis patients. Specific categories of sexual function have been included in several quality of life questionnaires, and narrower themes have been studied, such as the direct effect of dyspareunia on the sexual function of women with endometriosis [2].

To assist clinicians in diagnosing and treating endometriosis, numerous gynecological societies have released various guidelines. The range of the There are notable differences in the recommendations due to the complexity of this sickness and the available treatments. According to earlier research, the commonly used guidelines only have a 7% agreement rate, and none of them adhere to the Appraisal of Guidelines for Research and Evaluation II (AGREE-II) procedure [3].

This review compares eight commonly used endometriosis guidelines in order to provide an overview of endometriosis treatment.

Classification of fennel (*Foeniculam vulgare*)

Foeniculum uulgare Mill. finds extensive application in both the food sector and phytotherapy. Capillaceum and Piperiturn are its two subspecies. The latter is more practically significant. The three lower-rank taxonomic groups that comprise *F. vulgare subsp. capillaceum are var. vulgare* (Mill.) Thell. (bitter), var. duke (Mill.) Thell. (sweet), and var.

Florence Thell. (Mill.) Azoricurn. In addition to physical traits, each variety is known to have a unique essential oil makeup, with the most significant constituents being fenchone and (E)-anethole. The precise concentrations of these elements can range significantly among oils of various origins. The amount of fenchone in sweet fennel oil typically stays below 1% and seldom exceeds 5%, while in bitter varieties, it can reach 20%. In actual sweetness the amount of (E)-anethole in fennel oil ranges from 84 to 90%, but the amount in bitter fennel oil [4].

Nomenclature

English: Bitter fennel, common fennel, sweet fennel, wild fennel

Hindi: Badi, badishep, Bari saunf, badi, saunf, saunp, saunf, sonp

Botanical name: *Foeniculum vulgare* Mill

Taxonomy

Kingdom: Plantae,
Division: Tracheophyta,
Subdivision: Spermatophytina
Class: Magnoliopsida,
Order: Apiales,
Family: Apiaceae,
Genus: Foeniculum,
Species: vulgare

Limitation of current evidence treatment

The current gold standard for detecting endometriosis is thought to be laparoscopy. Two diagnostic methods are made possible by laparoscopy: direct endometriosis visualization and biopsy-based histological evaluation. Since a biopsy typically relies on a visual diagnosis, these are frequently combined.

Historically, access to therapy for individuals exhibiting pelvic discomfort and reproductive symptoms required a surgical and histological diagnosis of endometriosis. Therefore, the perceived necessity of using surgery as a diagnostic technique is probably a contributing factor in the delay in medicinal or surgical treatment of endometriosis. There has been a paradigm change to recommend empirical medicinal therapy before or instead of laparoscopy to individuals presenting with endometriosis symptoms, unless reproduction is a priority, in order to mitigate the negative implications of waiting for a surgical diagnosis.

Clinically history

Strenght: The diagnostic accuracy of common clinical symptoms of endometriosis (dysmenorrhea, pelvic pain, dyspareunia, and infertility) was evaluated in a comparative study of 90 women scheduled to undergo laparoscopy for possible endometriosis. A diagnosis of endometriosis was confirmed by laparoscopy and histopathology with a sensitivity of 76% and specificity of 58% for any of the four symptoms present on clinical history." In a recent study, 148 women with CPP (> 6 months) who were younger than 55

years old had their DTA of specific clinical symptoms assessed.

When compared to age-matched controls, a broader retrospective investigation of 5500 British women between the ages of 15 and 55 who had been diagnosed with endometriosis on record review revealed symptoms that are predictive of the diagnosis. Severe dysmenorrhea in infertile women, pelvic inflammatory disease, irritable bowel syndrome, excessive monthly bleeding, dyspareunia, postcoital bleeding, and/or a history of ovarian cysts were predictive symptoms. The odds ratio for endometriosis was shown to rise with the number of symptoms, rising from 5.0 when one symptom was present to 84.7 when seven or more symptoms were present.

Limitation

Although a clinical history is typically mentioned in an initial evaluation, its precision in predicting an endometriosis diagnosis is limited. First of all, a person's perception and communication of their symptoms might be quite subjective and varied. Based on the literature on chronic back pain, it can be inferred that the emotional experiences linked to chronic pain are diverse and can lead to a range of behavioral reactions, from avoidance to functional or adaptive behaviors.

Physical examination

Strenght

Visualization and palpation of endometriosis within the vagina certainly raises clinical suspicion that more extensive disease is present and can guide further assessment. From a resource perspective, a physical examination performed by a qualified clinician is timely and affordable because it is not dependent on the availability of surgical facilities or imaging modalities. The physical examination provides a non-invasive opportunity to detect endometriosis by visualization or palpation, as well as to assess sites of pain and organ mobility. Depending on the anatomic location of the disease, comparative data have shown that physical examination can accurately diagnose endometriosis.

The specificity of a positive evaluation for endometriosis in four different places on laparoscopy ranged from 89 to 100%. When it came to identifying endometriosis in the ovaries and bladder, the sensitivity of physical examination was as low as 23% and 25%, respectively, but it was quite high for finding endometriosis in the RVS (88%) and POD (70%).

Limitation

We think that a physical examination's ability to diagnose endometriosis depends on the examining clinician's experience. Furthermore, many persons with suspected endometriosis may not be able to tolerate physical examinations because of pelvic pain, and bimanual examinations may not be practical or appropriate for adolescents, people who are not sexually active, or people who have experienced prior sexual trauma.

The site of DE greatly affects the results of normal clinical examinations; according to one study, 80% of vaginal lesions were found on clinical examination, but 35% of DE in the rectum and 33% of DE in the USLs were found. Physical examination is a diagnostic modality that can only be used to detect DE; it cannot be used to distinguish between distinct disease subtypes, which limits its clinical utility. To the best of our knowledge, no research have evaluated the diagnostic accuracy of physical examination in detecting SE. Furthermore, it is challenging to evaluate organ mobility dynamically through physical examination (e.g., ovarian motility). The sensitivity for predicting POD obliteration is extremely low, especially when compared to the TVS uterine sliding sign, despite the fact that limited uterine motion and nodularity within the POD might be observed [5].

Pathophysiology of endometriosis

Endometriosis might have characteristics that resemble those of cancer. It is hypothesized that the pathological circumstances underlying the onset of endometriosis result increase in a number of biological functions linked to cell proliferation, survival, adhesion, invasion, and anoikis resistance. It is believed that angiogenesis and ECM remodeling are prevalent aspects of endometriosis progression, and that fibrosis and response play a role in the development of the process's clinical symptoms. The development of the clinical signs of this process is probably influenced by the mediators that lead to fibrosis and the inflammatory response.

Endogenous ligands shown to cooperate functionally in endometriosis are shown in Figure 1. Potential mechanism of NF-KB activation brought on by LPS (route 1) and oxidative stress (pathway 2), which leads to the upregulation of proinflammatory cascades via endogenous ligands/TLRs signalling (pathway 3). Three functional categories-induction of oxidative stress, response to inflammation, and TLR signalling-are associated with the bulk of the genes.

Gene pathway analysis identified "stress and defence response (so-called danger signals)" as a key mechanism among these three functional categories. To counteract damage from oxidative stress or LPS, most of the genes involved in the danger signals are amplified. This discovery aligns with the prevailing notion that the danger signal, which encompasses the immune response linked to TLRs, is a multifaceted network reaction of a tissue to endogenous ligands. The recognized biological reactions of endometriosis may be reflected in these functional categories.

Extremely high levels of oxidative stress buildup are thought to be typical indicators. Redox-sensitive transcription factors like p53 and NF-kB are genes that are changed in cellular reactions to oxidative stress. The transcription factor is activated by oxidative stress. The majority of reports of NF-kB have been made. Signaling mediated by NF-kB stimulates endometriotic cell invasion, inflammation, angiogenesis, proliferation, and anti-apoptosis.

NF-kB may therefore play a significant role in the pathophysiology of endometriosis.

Using gene ontology annotation tools, the genes that we previously reported [8] were categorized into functional groupings. Gene ontology makes it easier to comprehend data from high-throughput genomics and proteomics technologies by classifying gene functions based on biological processes, molecular functions, and cellular components. Numerous genes whose expression patterns link them to oxidative stress, inflammatory signaling, cell adhesion, protease, cell cycle, and growth factors-all of which are connected to cell adhesion, survival, antiapoptotic, and detoxification-are found among the gene lists upregulated in endometriosis.

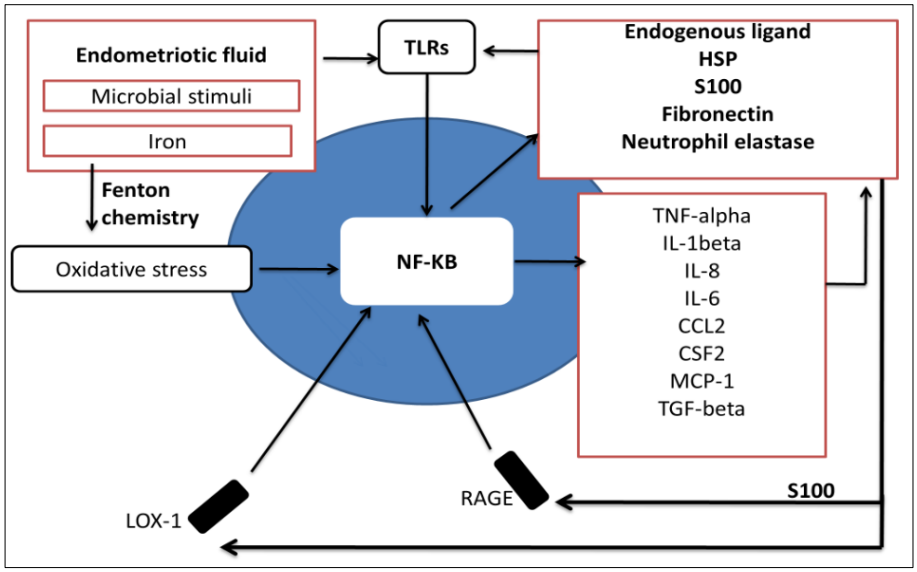

Fig 1: Overview of Pathophysiology of Endometriosis

Toll like receptor

The function of TLRs on endogenous ligands in the endometrium and endometriosis is covered in this review article. Healthy endometrium and endometriotic tissue had the highest expression of proteins including TLR3 and TLR4. Furthermore, TLR4 was found on monocytes, macrophages, and endometrial dendritic cells. TLRs are thought to play a crucial role in controlling climbing bacterial infections. Furthermore, HSPs, S100, fibronectin, fatty acids, oxidized LDL, neutrophil elastase, and hyaluronan are representative endogenous ligands for TLRs (also referred to as danger signals), and these are still not well described in endometriosis.

Heat shock protien

An extremely conserved class of intracellular chaperones are HSP proteins. The ATP-dependent HSP70 family of proteins aids in polypeptide folding. A substantial amount of data currently shows the function of Heat, hypoxia, ischemia, metabolic insults, oxidative stress, and heavy metals are only a few of the physico-biochemical stressors and stress situations that HSP overexpression protects tissue and cells against. HSPs including HSP60, HSP70, HSP70b0, HSP72, and HSP90 are crucial for macrophage activation as well as antigen presentation and cross-presentation.

Patients with endometriosis had a mean serum HSP70 level that was greater than that of controls, implying that elevated systemic oxidative stress is linked to endometriosis. Antigen-presenting cells' surface receptors (CD14, CD36, CD40, CD91, LOX-1, TLR2 and TLR4) are bound by HSP70, which increases the production of proinflammatory cytokines, chemokines, and nitric oxide as well as the expression of costimulatory molecules. By attaching to TLRs 2 and 4, HSP produced under oxidative stress promotes the production of inflammatory cytokines (TNF-a, IL-1b, and IL-6) in macrophages. Therefore, TLR4-mediated endometriosis development and pelvic inflammation may be induced by HSP.

S100

The S100 protein family regulates several physiological functions, including the advancement of the cell cycle, and has two EF-hand calcium binding motifs. According to Carlsson *et al*., ROS induces S100A7 and S100A9. Calgranulins, sometimes referred to as S100A8 and S100A9, are ligands for the RAGE receptor, through the RAGE-NA-kB axis, which contribute to modulating fibroproliferative remodeling.

Low density oxidised lipoprotein

Compared to controls, endometriosis-affected women had higher LDL levels. Rich in lipoproteins, especially LDL, the peritoneal fluid produces oxidized lipid components in an inflammatory environment that is populated by macrophages. Peritoneal mesothelial cells and endometrial cells produce monocyte chemotactic protein-1 (MCP-1) in response to oxidized LDL. Increased scavenger receptor activity, such as lectin-like oxidized LDL receptor (LOX-1), is a sign that macrophages are activated in endometriosis. Oxidized LDL uses a heterodimer of TLR4 and TLR6 to initiate inflammatory signaling and LOX-1, a scavenger receptor.

In addition to endometriosis, oxidative stress has been implicated in the development of numerous other illnesses, such as atherosclerosis, stroke, hypertension, cancer, memory loss, rheumatoid arthritis, and pregnancy difficulties. Because ROS overexpress oxidized LDL and induce insulin resistance, they may contribute to the development of type 2 diabetes mellitus. On the other hand, oxidized LDL may cause endothelial and macrophage mitochondria to produce ROS. Oxidative stress and the presence of oxidized LDL may also play a role in endometriosis, as they do in diabetes and atherosclerosis [6].

Pharmacological properties and therapeutic effect of fennel

Antimicrobial properties

Numerous infectious disorders caused by bacteria, fungi, viruses, and mycobacteria can be treated with fennel. Compounds include oleic acid, 1, 3-benzenediol, undecanal, linoleic acid, and 2, 4-undecadienal give fennel its antibacterial properties. 5-hydroxyfuranocoumarin, a compound found in fennel, plays a significant part in the plant's antibacterial function. *Enterococcus faecalis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas*

aeruginosa, *Salmonella typhi*, *Salmonella typhimurium*, and *Shigella flexneri* are all susceptible to the bactericidal effects of fennel aqueous extract.

According to a study, this plant extract significantly inhibits the growth of many bacteria, with the exception of Klebsiella pneumoniae and one strain of *Pseudomonas aeruginosa*.

Additionally, the MIC for the alcoholic and aqueous extracts of fennel seed was found to be between 5 and 15 mg/ml and 20 to 80 mg/ml, respectively, and statistical analysis demonstrated that the plant extract had a greater effect than conventional antibiotics. In addition to showing tremendous action against Helicobacter pylori and Campylobacter jejuni, the plant's essence had very significant antibacterial activity against foodborne pathogens such *Salmonella typhimurium*, *Escherichia coli*, Listeria, monocytogenes, and *Staphylococcus aureus*.

Antifungal action

Fennel extract exhibits antifungal properties against a range of fungal species, including dermatophytes, Aspergillus species, and Candida albicans. Additionally, a study on the antifungal impact of herbs revealed strong antifungal activity against *Aspergillus niger* and *Fusarium oxysporum*, two fungi found in food waste. For these molds, the fennel extract MIC was 250 and 750 micrograms per milliliter, respectively.

Another study demonstrated the antibacterial capabilities of dillapional, a derivative of fennel stem phenyl propanoid, against *Aspergillus niger*, *Bacillus subtilis*, and *Cladosporium cladosporioides*. Additionally, coumarin derivatives called scopoletin had antibacterial qualities against microorganisms, although they were not as potent as dillapional.

Activity of antioxidants

One of the best natural sources of antioxidants is fennel. Because of its high polyphenol and flavonoid content, this plant has the ability to block free radicals. This herb contains phenolic compounds with antioxidant properties, including kaempferol-3-O-glucoside, quercetin-3-O-galactoside, eriodictyol-7-orutinoside, caffeoylquinic acid, and rosmarinic acid. Additionally, fennel volatile oil exhibits potent antioxidant properties. The antioxidant activity of plant ethanolic and aqueous extracts is lower than that of their essence.

Anti-inflammatory properties

One of the fennel plant's pharmacological benefits is its anti-inflammatory properties. Studies have demonstrated the anti-inflammatory properties of fennel methanol extract. When taken orally, 200 mg per kg of fennel fruit methanol extract exhibits inhibitory effects on type 4 allergic reactions as well as acute and subacute inflammatory disorders. Furthermore, it reduced the catalase (CAT) and superoxide dismutase (SOD) activity. Additionally, it markedly raised HDL cholesterol plasma levels.

Activity that reduces anxiety

There have been reports of fennel crude extract's anxiolytic properties. Because it contains phytoestrogens, fennel is widely used therapeutically to treat problems related to estrogen insufficiency. Estrogens are hormones that seem to work through GABA A receptors to contribute to the phenomena of anxiety. According to a study's findings, plants that were exposed to more open arm time had a notable anxiolytic impact. Tamoxifen and picrotoxin (a GABA receptor antagonist) inhibited the anxiolytic effect.

Activity that protects the stomach

It has been established that fennel plant has strong protective effect on gastrointestinal problems. It was demonstrated that 65% of treated infants had no more colic after using fennel oil emulsions, which was much better than the control group. Al-Mofleh *et al*. looked into how the fennel plant affected stomach ulcers in one study.

The results demonstrated the plant's ability to prevent stomach ulcers. The herb also decreased the stomach's mucous membrane. Its antioxidant capability was thought to be responsible for these effects.

Estrogenic action

Since ancient times, fennel has been utilized as an estrogenic agent. Because of this characteristic, fennel promotes sexual desire, eases menstruation discomfort, helps childbirth, and boosts milk flow. The primary component of the fennel plant that has estrogenic effects is anattole. Studies have demonstrated that anthole polymers are the active medicinal ingredients dianthole and photoanatole.

Lipid and cardiovascular activity

Treatment with fennel methanol extract dramatically decreased plasma lipid levels, according to research on the extract's anti-cholesterol and anti-atherogenic properties.

The herb also shown significant anti-atherogenic properties. By lowering plasma and liver fats, it prevented the accumulation of fatty deposits in arteries, lowering triglycerides in fatty livers and improving blood flow in coronary arteries. This herb may therefore be used to treat cardiovascular diseases because to its hypolipidemic and anti-atherogenic properties. Additionally, the extract's intravenous administration dramatically lowered blood pressure without changing respiration or heart rate.

Rats with streptozotocin-induced diabetes were used in a study to assess the impact of fennel on lowering blood sugar. According to the findings, fennel extract reduces hyperglycemia in diabetic rats, which is partly explained by the herb's impact on the oxidation/restored system. Consequently, the pharmaceutical sector may exploit this plant to produce anti-diabetic medications. Additionally, fennel fruit methanol extract raised liver and muscle glycogen levels while lowering blood glucose and lipids.

Anti-cancer properties

It has been demonstrated that inflammation and cancer are related to TNF-α-dependent responses. It was discovered that fennel seed anethole inhibits the transcription factor NF-KB's ability to activate TNF-α. The findings demonstrated that anethole suppressed cellular reactions brought on by these cytokines, which may account for its function in preventing cancer. It also specified that the fennel with its antiangiogenic mechanisms inhibits prostate tumor xenograft

Activity that protects the liver

Research has shown that the fennel plant has a liver-protective function. Qiang *et al*. investigated the impact of

fennel extract in rats with liver damage brought on by carbon tetrachloride. According to study data, this extract decreased serum bilirubin, ALT (alanine amino transferase), ALP (alkaline phosphatase), and AST (aspartate aminotransferase) levels. Additionally, fennel's impact on lipid peroxidation in hepatic fibrosis-affected mice was examined.

Following fennel ingestion, TP, ALB, SOD, CAT, and GSH-PX activities rose whereas ALT, AST, and MDA content dramatically dropped. Based on the findings, it is possible to conclude that fennel may prevent hepatic fibrosis by regulating lipid peroxidation.

Activity that protects memory

Certain plants, such as fennel herbs, are thought to improve intelligence and memory. Thus, the impact of fennel extract on amnesiac rats' memory was investigated. The findings demonstrated that this extract had the ability to improve memory. Fennel extract's neurotropic and anti-acetylcholinesterase effects in mice were examined in the Joshi *et al*. study.

The results of this investigation demonstrated a substantial inhibition of acetylcholinesterase by fennel extract. Based on this study, it may be concluded that fennel may be utilized to treat cognitive diseases including Alzheimer's and dementia.

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Table 1: The potential mechanism of efficacy of some pharmacologic properties of *Foeniculum vulgare* [7]

Pharmacological Activity	Mechanism of action
Anti-microbial activity	Presence of active compound with anti-microbial activity such as oleic acid and coumarin in aqueous and alcoholic extract.
Antioxidant activity	Presence of antioxidant compounds such as flavonoid and phenol in aqueous and ethanolic extract.
Anti-inflammatory activity	The preventive effects of methanol extract against acute and sub-acute illness, type 4 allergic reaction through cyclooxygenase and lipoxygenase inhibition.
Anti-anxiety activity	Anxiolytic effects mediated by GABAergic and estrogen receptors
Gastro-protective activity	Regulation of intestinal muscle movement, treatment of gastrointestinal spasm and chronic colitis, protective effect on gastric ulcer, reduce the mucosal lining of the stomach.
Estrogenic activity	Presence of compound such as anatole effect on increasing milk secretion reduce menstruation pain, facilitate birth, primary dysmenorrheal and infertility
Anti-lipid activity	Hypolipidemic effect by reducing plasma triglyceride, total cholesterol, lowering LDL, decreased apolipoprotien B, increased HDL and increased apolipoprotien A-1.
Cardiovascular activity	Systolic blood pressure reduction, decreased excretion of sodium, potassium and water.
Anti-diabetic activity	The hypoglycemia effect by lowering blood glucose, increasing glutamine peroxide activity, increased levels and muscle glycogen.
Anti-cancer activity	Presence of active compound such as anethole, inhibitory effect on the activation of TNF-alpha, anti-angiogenic effect, and apoptotic and antitumor effects.
Hepato-protective activity	Decreased levels of AST, ALT, ALP, and bilirubin, reduction of proinflammatory cytokines such as TNF-alpha and CTGF in fibrosis.
Memory-protective activity	Inhibition effect on the acetyl cholinesterase enzyme.

Anethole: A Chief Bioactive Constituents

The physical-chemical characteristics of anethole

Figure 1 shows the anethole's chemical structure. Anethole involves the double bond outside the ring and can exist in both cis and trans isomers.

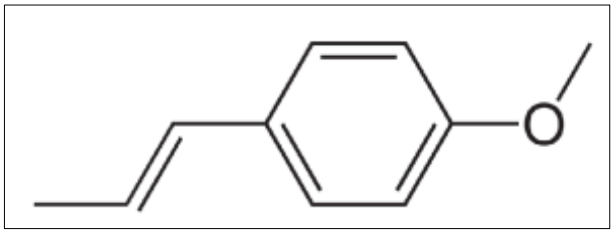

Fig 1: Chemical Structure of Anethole

The trans or E isomer is more prevalent and is the one that is favored for application.

Anethole has a sweet, anise-like flavor and is a transparent, colorless to amber liquid. Anethole has a significant solubility in ethanol but only a slight solubility in water. Because of this discrepancy, some liqueurs with an anise taste turn opaque when diluted with water. This results from a microemulsion forming on its own.

This occurs in nature: One kind of aromatic molecule that is commonly found in nature in essential oils is anethole. It contributes to the unique flavors of many other plants, including camphor, magnolia petals, liquorice (Fabaceae), anise myrtle (Myrtaceae), anise and fennel (both in the Apiaceae botanical family), and many others. Anise oil (80-90%), star anise oil (over 90%), and fennel oil (80%) all contain high levels of natural anethole.

Anethole pharmacokinetics

When taken orally, trans-anethole is quickly absorbed, almost entirely metabolized in the liver to produce conjugated metabolites, and then mainly eliminated in the urine. There is also some elimination as CO2 in expired air.

Traditional uses of anethelium

Include "dyspeptic complaints such as mild, spasmodic gastro-intestinal ailments, bloating, and flatulence" and

"catarrh of the upper respiratory tract." The antispasmodic, secretolytic, secretomotor, and antibacterial properties of aniseed's essential oil account for a large portion of its medicinal use.

Anise has been used in traditional medicine to treat upset stomachs, "runny noses, " expectorants, diuretics, hunger stimulants, and productive coughs. Anise is used by women to ease childbirth, induce menstruation, relieve menstrual pain or discomfort, boost sex drive, and improve milk flow during nursing. Anise is used by males to address "male menopause" symptoms. Treatments for seizures, nicotine addiction, insomnia, asthma, and constipation are among its additional applications. Psoriasis, scabies, and lice can all be treated with anise applied topically.

Anethole pharmacological activities

Antioxidant action

A modified thiobarbituric acid reactive species assay and a spectrophotometric detection of hydroperoxydienes from linoleic acid in a micellar system were used to assess the antioxidant capabilities of fennel oil. The results were similar to those of the reference antioxidants butilated hydroxytoluene and α-tocopherol. In the linoleic acid system, fennel seed water and ethanol extracts demonstrated 99.1% and 77.5% inhibition of peroxidation, respectively, which was higher than the same amount of α-tocopherol (36.1%).

Insecticidal, antimicrobial, antifungal, and antihelmintic properties

Strong antibacterial qualities make anethole effective against fungus, yeast, and bacteria. In viral suspension tests, all identified chemicals including star anise essential oil directly inactivate free virus particles, demonstrating anti-HSV-1 efficacy. Viral infectivity was decreased by >99% by star anise oil.

A variety of bacteria, including *Escherichia coli* and *Staphylococcus aureus*, were inhibited in their growth by an aniseed acetone extract, which also shown antifungal efficacy against Candida albicans and other species.

Salmonella enteritidis was activated *in vitro* by anise oil (0.2%) alone. Using the agar dilution method, aniseed essential oil prevented the development of *Salmonella typhimurium* (MIC: 2.0%), *Staphylococcus aureus* (MIC: 0.25%), *Escherichia coli* (MIC: 0.5%), and Candida albicans (MIC: 0.5%).

On the eggs and larvae of the sheep gastrointestinal nematode Haemonchuscontortus, anethole exhibits antihelmintic activity *in vitro*.

As a fumigant, anethole has a stronger insecticidal effect than when used as a contact agent. When used as a fumigant, (E)-anethole effectively combats the cockroach Blattella germanica. An efficient insect repellant for mosquitoes is an anethole.

Expectorant and secretolytic effects

In the first two hours following intragastric administration of an essential oil solution in 12% ethanol at a dose of 50 mg/kg b.w. to anesthetized guinea pigs, the respiratory tract fluid increased three to six times. In a related study, rats under anesthesia who received an oral dose of the oil at 0.0015 ml/kg saw a 28% increase in respiratory tract fluid.

Cats also showed comparable outcomes. Cats given an intragastric emulsion of two drops of the essential oil experienced an increase in mucus secretion in their airways and ciliary mucus clearance, which was previously suppressed by opium alkaloids.

Effect of spasmolysis on smooth muscles that are tensed

According to pharmacological data, aniseed alcoholic extracts and essential oil significantly relax the smooth muscles of the trachea and ileum when they are contracted by a number of contraction-inducing substances (such as metacholine and carbachol).

Anti-inflammatory and antinociceptive properties

Solutions of trans-anethole injected into the conjunctival sac in the rabbit conjunctival reflex test increased the number of stimuli needed to elicit the conjunctival response in a concentration-dependent manner ($p<0.01$); the effect was similar to that of procaine.

In inflammatory pain models, the impact of anethole was assessed. In the second phase of the formalin-induced paw kicking test, the test with glutamate injected beneath the ventral surface of the left hind paw, the writhing model induced by intraperitoneal application of acetic acid, and the pain induced by complete Freund adjuvant (CFA) injected into the plantar surface of the hind paw, anethole (62.5, 125, 250, and 500 mg/kg) demonstrated an antinociceptive effect. However, in none of the tested doses, anethole was able to shorten the latency time on the hot plate or reduce the frequency of flinches during the formalin test's early phase.

Activity that protects the stomach

In rats given ethanol (90%, 1 ml) to induce ulcerogenesis, the gastroprotective effects of F. vulgare essential oil and anethole at doses of 50 and 100 mg/kg were investigated. Anethole and fennel oil had a strong gastroprotective effect against the erosive damage brought on by ethanol. Their antiplatelet and vasorelaxant properties may be responsible for their comparable antiulcer action by preserving a healthy blood supply in the stomach mucosa. They could, in fact, stop the disruption of the stomach circulation brought on by ethanol, which resulted in local vasocongestion, vascular stasis, and mucosal injury brought on by an excess of free radicals derived from oxygen. In the ethanol-induced ulcer mode, pretreatment with anethole (30 and 300 mg/kg) markedly increased the production of mucus by the stomach mucosa.

Effects of estrogen

Compared to 0.5 g/kg in controls and 3 g/kg in animals given estradiol valerate subcutaneously at 0.1 µg/rat/day, trans-anethole given orally to immature female rats at 80 mg/kg for three days dramatically raised uterine weight to 2 g/kg ($p<0.001$).

These findings validated trans-anethole's estrogenic action. It had no anti-estrogenic, progestational, anti-progestational, androgenic, or anti-androgenic activity, according to other tests.

Trans-anethole's estrogenogenic activity at high doses has been assessed by a sensitive and specific bioassay employing human estrogen receptor-expressing recombinant yeast cells. Epidemiological evidence pertaining to the widespread consumption of aniseed alcoholic beverages does not support the estrogenic activity reported for trans-anethole for aniseed alcoholic extracts.

Toxicology to reproduction

When given orally to adult female rats on days 1-10 of pregnancy, trans-anethole demonstrated dose-dependent anti-implantation action. Transanetholes given at 50, 70, and 80 mg/kg inhibited implantation by 33%, 66%, and 100%, respectively, in contrast to control animals, all of which produced normal pups at term. The 80 mg/kg dosage was used in other studies at various phases of pregnancy.

Rats given trans-anethole on days 1-2 of pregnancy experienced normal implantation and delivery; rats given anethole on days 3-5 of pregnancy experienced complete inhibition of implantation; and three out of five rats given trans-anethole on days 6-10 of pregnancy did not deliver at term. No severe deformities in the kids in any of the groups were noted. The findings showed that trans-anethole had antifertility properties. The reduced degree of delivery in the days 1-2 group (lack of antizygotic action). It was believed that the group from days 6-10 showed early abortifacient action.

Sedative action

Simultaneous intraperitoneal delivery of essential oil at 50 mg/kg extended the mice's pentobarbital-induced sleeping period by 93.5%; trans-anethole produced comparable effects.

Anethole's safety and toxicity

Although the evidence is weak and usually interpreted as proof that anethole is not a carcinogen, it is linked to a modest rise in liver cancer in rats. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated anethole and discovered that its pharmacologic properties included hypnotic, analgesic, and anticonvulsant effects, as well as a decrease in motor activity and a decrease in body temperature. According to the JECFA summary of these assessments, anethole has no safety risks when used as a flavoring ingredient at the current intake levels. Anethole is somewhat hazardous in high concentrations and can irritate skin [8].

Mechanistic insights into anethole's role in endometriosis

Pure anethole has not been tested in clinical settings for endometriosis. There are, nonetheless, relevant clinical data. Studies have examined the effects of fennel oil, which is high in trans-anethole, on menopausal symptoms and dysmenorrhea. Fennel oil reduced menstruation discomfort in a short clinical trial (30 women, 3 cycles), most likely because of its antispasmodic and anti-inflammatory properties. Anethole's source, anise, has been used to treat menstruation pain and other feminine problems, according to a recent review, which attributed its effectiveness to its analgesic and anti-inflammatory properties [9]. Crucially, aromatherapists advise against using anethole for endometriosis and estrogen-dependent malignancies because to its estrogenic nature [10, 11]. This emphasizes the necessity of thorough assessment.

The preclinical data indicates that anethole addresses many pathogenic mechanisms in endometriosis by inhibiting NF-κB and inflammatory cytokines (TNF-α, IL-1β, IL-6), [12, 13] suppressing COX-2 and PGE_2 [14, 15]. alleviating oxidative stress, [16] downregulating VEGF and MMPs, [17] and modulating immunological equilibrium (↑IL-10). The multifunctional effects of anethole align with established endometriosis drivers, positioning it as a potential for future investigation. Thorough clinical research is essential to evaluate effectiveness and safety, particularly due to its estrogenic characteristics.

Current Evidence and Related Condition

Fennel, which is rich in anetholes, has been tested for menstrual pain in a number of studies. Fennel considerably decreased primary dysmenorrhea pain, according to a 2020 meta-analysis (12 RCTs, n≈500), and its effects were equivalent to those of conventional NSAIDs [18]. In fact, aggregated studies indicated fennel was as effective as conventional medications for pain alleviation, and substantially superior than placebo. According to one Iranian RCT, for instance, fennel essential oil (the main ingredient in trans-anethole) considerably reduced the severity of menstruation discomfort, most likely by relaxing the uterine muscles. Overall, these clinical investigations indicate that fennel containing anethole reduces dysmenorrhea with effectiveness comparable to that of conventional analgesics [19].

Advantages of Fennel-Based Therapy

Twelve RCTs that examined fennel's ability to lessen pain in primary dysmenorrhea were found. When compared to a placebo, the meta-analysis showed that fennel was just as effective as traditional medication therapy in lowering pain in primary dysmenorrhea. However, it was shown that fennel considerably outperformed a placebo in terms of pain relief. We are unable to make a determination about the safety of fennel in the treatment of primary dysmenorrhea since the majority of the trials did not evaluate adverse events.

Based on nine trials, a recent analysis assessed fennel's effectiveness and found that fennel extract reduced menstruation discomfort. Nevertheless, one non-RCT and one duplicate article were included in this review.

Furthermore, this assessment combined the data without attention to controls. By disregarding the clinical variability, this might inflate the effectiveness and spread false information. Five papers were examined in the second systematic review, which concluded that more research on the effects of fennel was required. However, our study provided stronger evidence since it contained over twice as many papers as the second review. The third evaluation, which comprised 13 trials, found that fennel had a favourable impact on primary dysmenorrhea.

As of right now, there isn't enough solid information to conclude that fennel helps persons with primary dysmenorrhea, nor is there any indication of how much of a benefit it could have. More reliable results are undoubtedly preferred. However, our findings demonstrate that fennel is just as effective as traditional medication therapy and may be suggested as a successful treatment. Given the above-discussed limitations, this conclusion, which is based on the findings in this review, is made cautiously [20].

Research Gap and Future Directions

Existing studies on medicines that include anethole (such as dill, fennel, and anise) are often small, diverse, and subject to a moderate risk of bias. According to a recent comprehensive analysis of fennel trials, few of the studies reported proper randomization, blinding, or allocation concealment, and the majority had relatively small sample

numbers (often less than 50 per arm). There were few real placebo-controlled studies, and the majority of RCTs merely evaluated fennel or dill against active medications (NSAIDs, for example) or no-treatment controls. Pooled estimates are therefore vulnerable to fresh data and underpowered. Concerns regarding generalizability are further raised by the fact that the great majority of trials have only been carried out in one area (Iran/Middle East) and frequently on a small number of student demographics. Almost no trials consistently record side effects, and treatment durations and outcomes vary (from single-dose regimens to multi-cycle usage). For instance, one RCT indicated that "further studies regarding side-effects" were required, while finding that dill seed decoction was just as efficient as mefenamic acid. Overall, present clinical data is minimal but promising; confidence is undermined by small sizes, variable formulations (capsules, teas, oils, combinations), and methodological flaws (limited blinding, absence of study registration).

There is a need for robust clinical studies to fill these gaps. We advise conducting extensive, multicenter RCTs using regulated dosages and formulations of anethole (or pure fennel oil) together with placebo controls. Validated pain measures and a sufficient number of participants-ideally several hundred-are essential for successful trials. To remove prejudice, blinding measures must be taken, such as using faux scent or placebo pills. Additionally required are dose-response studies, such as head-to-head comparisons of various anethole dosage levels. Comparative studies against common NSAIDs, such as mefenamic acid and ibuprofen, would also demonstrate synergy or non-inferiority. Quality-of-life indicators, any adverse effects, and the degree and duration of pain should all be included in outcome measurements. Importantly, adverse occurrences need to be evaluated and documented in a methodical manner. Every study must adhere to CONSORT reporting requirements and be prospectively registered. According to one assessment, fennel and anise frequently seemed "as effective as conventional drug therapies" for treating dysmenorrhea; nevertheless, recommendations are still hesitant given the absence of safety evidence. Generalizability will be enhanced by ensuring ethnic and geographic variety, not just among Middle Eastern people. In conclusion, strong criteria should guide the design of future clinical research: NSAID/placebo controlled, double-blind, randomized, with a sufficient sample size, precise dosage, and safety monitoring [21].

Conclusion

Anethole, the main component of fennel (*Foeniculum vulgare*), exhibits multimodal effects on pathways essential to the pathophysiology of endometriosis. Preclinical research shows strong anti-inflammatory effects: in animal models, anethole inhibits NF-κB activation and decreases proinflammatory mediators (TNF-α, IL-6, and MMP-9)[22] and alters immunological balance by decreasing IL-17 and raising IL-10 with a change in Th17/Treg cells.[23] Flavonoids and phenolics, which are abundant in fennel extracts, are antioxidants that scavenge reactive oxygen species and prevent lipid peroxidation [24]. Furthermore, by inhibiting MMP-2/9 expression and downregulating VEGF/VEGFR-2 signalling, anethole has anti-angiogenic properties that may prevent ectopic lesions from neovascularizing. The hormonal function of fennel is complicated. Although trans-anethole is a poor phytoestrogen *in vitro*, [25] fennel strangely lowers systemic estradiol while increasing progesterone levels in mouse experiments [26]. Therefore, fennel/anethole targets angiogenesis, oxidative stress, inflammation, and oestrogen signalling-all of which are important factors in the development of endometriosis.

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