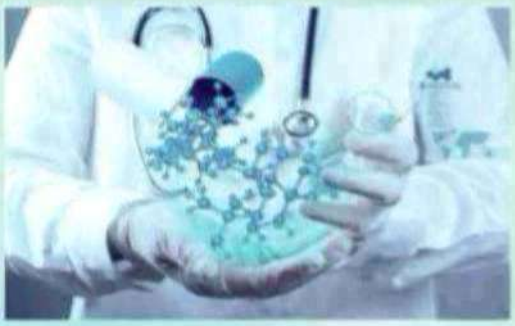
New Day in Medicine
Новый День в Медицине
NDM

TIBBIYOTDA YANGI KUN

Ilmiy referativ, marifiy-ma'naviy jurnal



AVICENNA-MED.UZ

ISSN 2181-712X.
EiSSN 2181-2187

12 (86) 2025

ТИББИЁТДА ЯНГИ КУН
НОВЫЙ ДЕНЬ В МЕДИЦИНЕ
NEW DAY IN MEDICINE

Илмий-рефератив, маънавий-маърифий журнал
Научно-реферативный,
духовно-просветительский журнал

УЧРЕДИТЕЛИ:

БУХАРСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ ИНСТИТУТ
ООО «ТИББИЁТДА ЯНГИ КУН»

Национальный медицинский исследовательский центр хирургии имени А.В. Вишневского является генеральным научно-практическим консультантом редакции

Журнал был включен в список журнальных изданий, рецензируемых Высшей Аттестационной Комиссией Республики Узбекистан (Протокол № 201/03 от 30.12.2013 г.)

12 (86)

2025
декабрь

www.bsmi.uz
https://newdaymedicine.com E:
ndmuz@mail.ru
Тел: +99890 8061882

Received: 20.11.2025, Accepted: 06.12.2025, Published: 10.12.2025

УДК 615.322

CHEMICAL COMPOSITION, BIOLOGICAL ACTIVITIES, AND THE PROMISE OF BIOACTIVE PEPTIDES IN FOENICULUM VULGARE L.: A COMPREHENSIVE REVIEW

Ermatov I.S., Sattorov S.R., Sumairemu S., Yasen M., Mustafaev U.G.

Xinjiang Medical university, School of Pharmacy, Urumqi, 830011, PR China.

✓ ***Resume***

Foeniculum vulgare Mill. (fennel), a prominent member of the Apiaceae family, is a versatile plant with a rich history in traditional medicine systems worldwide. This review provides a critical and up-to-date analysis of the phytochemical composition and the broad spectrum of pharmacological activities of F. vulgare. The plant's bioactivity is attributed to its diverse array of secondary metabolites, including phenylpropenes (trans-anethole, estragole), monoterpenes (fenchone, limonene), flavonoids (quercetin, rutin), phenolic acids, and fatty acids. Modern scientific investigations have validated its antioxidant, antimicrobial, anti-inflammatory, gastroprotective, hepatoprotective, and estrogen-like effects. Emerging evidence also highlights its anticancer potential through mechanisms such as apoptosis induction and cell cycle arrest. A significant advancement in the field is the application of nanotechnology for the encapsulation and targeted delivery of fennel bioactives, which enhances their bioavailability, stability, and therapeutic efficacy. This review consolidates recent findings from 2020 to the present, addressing the pharmacological mechanisms, safety profile, and potential drug interactions. It also concludes by identifying an important gap in the literature – the unexplored peptide profile of fennel – and proposes that the isolation and characterization of these peptides represent a vital future direction for research.

Keywords: Foeniculum vulgare, fennel, essential oil, trans-anethole, phytochemistry, pharmacology, nanotechnology, clinical evidence, safety.

FOENICULUM VULGARE L. DAGI KIMYOVIY TARKIBI, BIOLOGIK FAOLIYATI VA BIOAKTIV PEPTIDLARNING ISTE'MOLI: KOMPLEKS SHARH

Ermatov I.S., Sattorov S.R., Sumairemu S., Yasen M., Mustafaev U.G.

Xinchjon tibbiyot universiteti, Farmatsiya maktabi, Urumchi, 830011, Xitoy PR.

✓ ***Rezyume***

Foeniculum vulgare tegirmoni (arpabodiyon), Apiaceae oilasining taniqli a'zosi, butun dunyo bo'ylab an'anaviy tibbiyot tizimlarida boy tarixga ega ko'p qirrali o'simlikdir. Ushbu sharh F. vulgare ning fitokimyoviy tarkibi va keng farmakologik faolligining tanqidiy va zamonaviy tahlilini taqdim etadi. O'simlikning bioaktivligi uning fenilpropenlar (trans-anetol, estragol), monoterpenlar (fenxon, limonen), flavonoidlar (kversetin, rutin), fenolik kislotalar va yog 'kislotalari kabi turli xil ikkilamchi metabolitlari bilan bog'liq. Zamonaviy ilmiy tadqiqotlar uning antioksidant, mikroblarga qarshi, yallig'lanishga qarshi, gastroprotektiv, gepatoprotektiv va estrogenga o'xshash ta'sirini tasdiqladi. Yangi dalillar, shuningdek, apoptoz induksiyasi va hujayra siklining to'xtashi kabi mexanizmlar orqali uning saratonga qarshi potentsialini ta'kidlaydi. Ushbu sohadagi muhim yutuq - bu arpabodiyon bioaktiv moddalarini kapsulalash va maqsadli yetkazib berish uchun nanotexnologiyani qo'llash bo'lib, bu ularning biomavjudligini, barqarorligini va terapevtik samaradorligini oshiradi. Ushbu sharh 2020-yildan hozirgi kungacha bo'lgan so'nggi topilmalarni birlashtiradi, farmakologik mexanizmlar, xavfsizlik profili va potentsial dori vositalarining o'zaro ta'sirini ko'rib chiqadi. Shuningdek, u adabiyotdagi muhim bo'shliqni - arpabodiyonning o'rganilmagan peptid profilini - aniqlash bilan yakunlanadi va bu peptidlarni ajratish va tavsiflash tadqiqotlar uchun muhim kelajakdagi yo'nalish ekanligini taklif qiladi.

Kalit so'zlar: Foeniculum vulgare, arpabodiyon, efir moyi, trans-anetol, fitokimyo, farmakologiya, nanotexnologiya, klinik dalillar, xavfsizlik.

Introduction

1.1 Botanical profile and historical context

Foeniculum vulgare Mill., commonly known as fennel, is a hardy, perennial, umbelliferous herb characterized by its erect, glaucous green stems, finely dissected pinnate leaves, and compound umbels of small yellow flowers, typically reaching heights of 0.5 to 2.5 meters [1]. The plant produces dry, schizocarpic fruits, often erroneously referred to as seeds, which are the primary source of its prized essential oil. Indigenous to the Mediterranean region, fennel has become naturalized and is extensively cultivated in temperate zones across the world, including Europe, Asia, North America, and parts of Africa.

The history of fennel's use is as rich and extensive as its phytochemistry. It was well-known to the ancient Egyptians, Greeks, Romans, and Chinese. In Greek mythology, Prometheus used a stalk of fennel to steal fire from the gods. Hippocrates and Dioscorides prescribed it for a range of ailments, from infantile colic to visual disorders. Within Ayurvedic medicine, known as Saunf or Moti saunf, it is a critical component of digestive formulations and is considered a Madhurashaka (sweet herb) with cooling properties. Traditional Chinese Medicine employs fennel (Xiao Hui Xiang) to warm the kidneys, disperse cold, and alleviate pain, particularly in the lower abdomen [2]. Different plant parts—seeds, leaves, roots, and even pollen—have been utilized for their therapeutic properties, demonstrating the plant's integral role in global ethno pharmacology.

1.2 Modern resurgence of Interest

The 21st century has witnessed a paradigm shift towards natural products, driven by consumer demand for "clean-label" ingredients, concerns about the side effects of synthetic drugs, and a growing body of scientific evidence supporting the efficacy of herbal medicines. In this context, F. vulgare has experienced a significant resurgence. It is no longer viewed merely as a culinary spice but as a source of potent bioactive compounds for functional foods, nutraceuticals, and cosmeceuticals.

Modern pharmacological research has sought to deconstruct the traditional claims, identifying the active constituents and elucidating their mechanisms of action at the molecular level. Furthermore, challenges associated with the application of plant-derived compounds—such as poor solubility, instability, and low systemic bioavailability—have spurred innovative solutions, most notably through the application of nanotechnology. This review aims to synthesize the substantial body of research on F. vulgare published from 2020 onwards. It will provide a critical analysis of its complex phytochemistry, validate its pharmacological activities through mechanistic insights and clinical evidence, explore cutting-edge Nano-formulation strategies, and discuss the associated safety and regulatory landscape to chart a course for its future development as a evidence-based therapeutic agent.

2. PHYTOCHEMICAL COMPOSITION OF FOENICULUM VULGARE

The therapeutic potential of fennel is a direct consequence of its intricate and dynamic phytochemical profile. This profile is not static but is significantly influenced by a multitude of factors, leading to substantial variability in the concentration and presence of bioactive compounds.

2.1. Factors Influencing Chemical Variability

Chemo types: The primary genetic classification distinguishes between sweet fennel (F. vulgare var. dulce), characterized by high levels of trans-anethole (>80%), and bitter fennel (F. vulgare var. vulgare), which contains substantial amounts of fenchone [3].

Agro-Climatic and Edaphic Factors: Geographical origin, altitude, soil composition, sun exposure, and rainfall patterns profoundly impact the biosynthesis of secondary metabolites. For instance, fennel from Southern Europe typically has a sweeter profile (high anethole), while Northern European varieties are more bitter (high fenchone) [4].

Plant Part: The distribution of compounds is highly organ-specific. Essential oil is concentrated in the fruits (seeds), phenolic compounds are abundant in the seeds and leaves, while the roots may contain unique compounds like dillapiole and specific polysaccharides [5].

Post-Harvest Processing: The method of drying (sun-drying vs. oven-drying), storage conditions (light, temperature, humidity), and the extraction technique (hydro distillation, supercritical CO_2, microwave-assisted extraction) drastically affect the yield and composition of the extracts [6].

2.2. Essential Oil Volatiles

The essential oil, concentrated in the fruits (seeds), is the most characterized component. Gas chromatography-mass spectrometry (GC-MS) analyses consistently identify **trans-anethole** (40–90%) as the predominant compound, responsible for the sweet aroma and key pharmacological actions. **Estragole** (methyl chavicol; 10–20%) contributes to the aroma but poses genotoxicity concerns at high doses. **Fenchone** (10–20%), a bicyclic monoterpene, imparts a camphoraceous note and spasmolytic activity. Minor constituents like **limonene**, **α-pinene**, and **β-pinene** further contribute to the oil's antioxidant and antimicrobial properties. Chemotypes (e.g., sweet vs. bitter fennel) and geographical origin significantly alter these ratios.

Trans-Anethole: This E-isomer of anethole is the cornerstone of fennel's bioactivity and aroma. It is metabolized in the liver to various compounds, including anisaldehyde and estragole. Its estrogenic activity is attributed to its structural similarity to the neurotransmitter dopamine and the hormone estrogen, allowing it to bind to relevant receptors [7].

Estragole (Methyl Chavicol): While a natural component, estragole is a safety concern. It is metabolized to 1'-hydroxyestragole, which can be further activated to a DNA-reactive carbocation. However, the risk is considered dose-dependent. The European Food Safety Authority (EFSA) and other bodies emphasize that typical dietary exposure poses a negligible risk, but caution is advised for concentrated supplements and essential oils [8].

Fenchone: This ketone terpene provides the characteristic camphoraceous odor of bitter fennel. It is a key marker for quality control and contributes significantly to the antispasmodic effects on smooth muscle, likely through calcium channel blockade [9].

The non-volatile phenolic fraction is primarily responsible for fennel's potent antioxidant capacity. Advanced techniques like HPLC-DAD-ESI/MS^n have identified a diverse profile.

Flavonols:Quercetin-3-O-glucuronide, rutin (quercetin-3-rutinoside), and various kaempferol glycosides (e.g., kaempferol-3-O-glucoside, kaempferol-3-O-rutinoside) are the most abundant. These compounds are powerful free-radical scavengers and metal chelators [10].

Flavones: Apigenin and luteolin, along with their glycosides (e.g., apigenin-7-O-glucoside), have been identified, contributing to anti-inflammatory and anticancer activities.

Flavan-3-ols:Catechin and epicatechin are present, supporting gastrointestinal health and vascular function.

Phenolic Acids: Hydroxycinnamic acid derivatives, such as chlorogenic acid, caffeic acid, and ferulic acid, are significant contributors to the overall antioxidant power of aqueous and hydroalcoholic extracts [11].

The Total Phenolic Content (TPC) and Total Flavonoid Content (TFC) are highest in seed extracts, followed by leaf and root extracts, directly correlating with their antioxidant potential in assays like DPPH, ABTS, and FRAP.

2.3. Phenolic Compounds and Flavonoids

2.4. Fixed Oils, Fatty Acids, and Phytosterols

Fennel seeds contain 12-18% of a fixed (non-volatile) oil. The fatty acid profile is distinctive:

Petroselinic Acid (C18:1 n-12): This unusual omega-12 monounsaturated fatty acid can constitute up to 60-80% of the total fatty acids and is a chemotaxonomic marker for the Apiaceae family. It has shown potential in inhibiting the growth of certain cancer cells and modulating inflammatory pathways [12].

Oleic Acid (C18:1 n-9): A common monounsaturated fat with recognized cardiovascular benefits.

Linoleic Acid (C18:2 n-6): An essential polyunsaturated fatty acid.

Palmitic Acid (C16:0): A saturated fatty acid.

The fixed oil also contains significant amounts of phytosterols, particularly β-sitosterol, stigmasterol and campesterol, which contribute to the observed hypolipidemic effects by competing with dietary cholesterol for absorption [13].

2.5. Other Bioactive Constituents

Polysaccharides:Recent studies have isolated water-soluble polysaccharides from fennel seeds with demonstrated prebiotic activity, stimulating the growth of beneficial gut bacteria like *Lactobacilli* and *Bifidobacteria*, and exhibiting immunomodulatory properties [14].

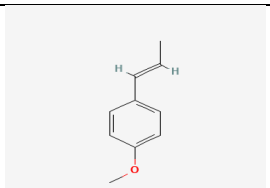
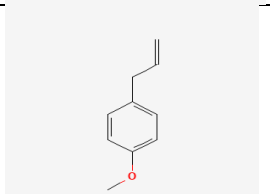
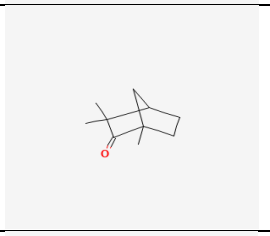
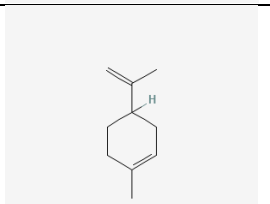
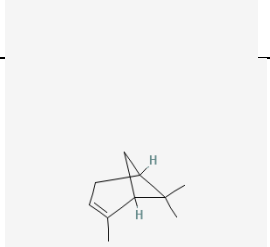
Furanocoumarins:Compounds like bergapten, imperatorin, and psoralen are present in trace amounts. They are known for their phototoxic effects but are also investigated for their potential in treating skin conditions like psoriasis (PUVA therapy) [15].

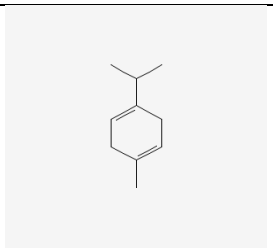
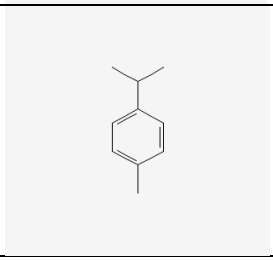
Alkaloids and Saponins: While present in minor quantities, these classes may contribute to the overall bioactivity, though they are less characterized than the volatile and phenolic components.

Notably, one major class of nitrogen-containing compounds, bioactive peptides, remains largely uninvestigated in fennel, representing a significant gap in the comprehensive phytochemical profiling of this plant.

Table 1: Major and Minor Volatile Constituents of Fennel Essential Oil

(The chemical structures were obtained from the PubChem database.)

Compound	Chemical structure	Chemical class	Content range (%)	Key biological activities
Trans-Anethole		Phenylpropene	40 – 90	Estrogenic, antimicrobial, anti-inflammatory, spasmolytic
Estragole		Phenylpropene	1 – 20	Flavoring, potential genotoxicity at high doses
Fenchone		Bicyclic monoterpene	5 – 25	Antispasmodic, antioxidant, bitter flavor marker
Limonene		Monoterpene	1 – 7	Antioxidant, anti-inflammatory, chemopreventive
α-Pinene		Monoterpene	1 – 5	Antimicrobial, anti-inflammatory, bronchodilator

γ-Terpinene		Monoterpene	0,1 – 3	Antioxidant
p-Cymene		Monoterpene	0,1 – 2	Precursor to other terpenes, antimicrobial

3. PHARMACOLOGICAL ACTIVITIES: FROM TRADITION TO EVIDENCE-BASED SCIENCE

3.1. Antioxidant Activity: The First Line of Defense

Oxidative stress, resulting from an imbalance between free radicals and antioxidants, is implicated in aging and numerous chronic diseases. Fennel extracts demonstrate robust antioxidant activity in vitro.

Mechanisms: The primary mechanism is the direct scavenging of reactive oxygen species (ROS) and nitrogen species (RNS) like DPPH, $ABTS^{+}$, and nitric oxide (NO). Flavonoids and phenolic acids donate hydrogen atoms or electrons, neutralizing these radicals. They also act as metal chelators, preventing Fenton reactions that generate highly reactive hydroxyl radicals [16].

Evidence: Multiple studies report IC_{50} values for fennel seed extracts in DPPH assays ranging from 20 to 150 μg/mL, often comparable to synthetic antioxidants like BHT and ascorbic acid. The reducing power, as measured by FRAP assay, is also significant and strongly correlates with the Total Phenolic Content (TPC) [17]. This antioxidant capacity underpins many of its other protective effects, including hepatoprotection, neuroprotection, and anti-aging properties in cosmetics.

3.2. Antimicrobial and Antifungal Activities: A Natural Preservative

Fennel essential oil exhibits broad-spectrum antimicrobial activity, making it a promising natural preservative and therapeutic agent.

Mechanism of Action: The hydrophobic nature of the essential oil allows it to partition into the lipid bilayer of microbial cell membranes, disrupting its structure and integrity. This leads to increased membrane permeability, leakage of vital intracellular constituents (ions, ATP, nucleic acids), and ultimately, cell death. Trans-anethole and estragole are the primary agents responsible for this membrane damage [18].

Evidence:

Antibacterial:Fennel oil is effective against both Gram-positive (e.g., Staphylococcus aureus, Bacillus subtilis) and gram-negative (e.g., Escherichia coli, Salmonella typhimurium) bacteria, with Minimum Inhibitory Concentrations (MICs) typically between 0,5 and 2,0 μL/mL [19].

Antifungal:It shows potent activity against pathogenic fungi like Candida albicans and dermatophytes (Trichophyton spp., Microsporum spp.), inhibiting both mycelial growth and spore germination [20].

Food Preservation: Incorporating fennel oil (0,5-2%) into edible coatings or directly into food matrices (dried meat products) has been shown to significantly extend shelf life by suppressing microbial growth and delaying lipid oxidation [21].

3.3. Anti-inflammatory and Analgesic Effects: Molecular Targets

The traditional use of fennel for inflammatory conditions like arthritis and for pain relief is supported by modern pharmacology.

Mechanisms:

Cytokine Suppression:Fennel extracts downregulate the production of key pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and IL-1β.

Inhibition of Inflammatory Mediators: They suppress the expression of inducible nitric oxide synthase (iNOS), reducing NO production, and cyclooxygenase-2 (COX-2), decreasing prostaglandin E2 (PGE2) levels.

Signaling Pathway Modulation:Bioactives like anethole and quercetin inhibit the activation of the master transcription factor NF-κB and the MAPK (p38, JNK, ERK) pathways, which are central to the inflammatory response [22].

Analgesic Evidence: In vivo models (acetic acid-induced writhing, formalin test, hot plate test) consistently show that fennel essential oil and extracts produce significant, dose-dependent analgesia. The effect is often comparable to non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin or diclofenac, suggesting its potential for managing mild to moderate inflammatory pain [23].

3.4. Anticancer Potential: Pro-apoptotic and Anti-proliferative Mechanisms

Recent research has unveiled the potential of fennel as a complementary agent in cancer therapy.

Mechanisms:

Apoptosis Induction: Fennel extracts and isolated compounds (e.g., anethole, quercetin) trigger programmed cell death in various cancer cell lines (breast, liver, colon, cervical) by upregulating pro-apoptotic proteins (Bax, Bak), downregulating anti-apoptotic proteins (Bcl-2, Bcl-xL), and activating caspase-3 and -9 [24].

Cell Cycle Arrest: They halt the uncontrolled proliferation of cancer cells by inducing arrest at specific cell cycle checkpoints, primarily G1/S or G2/M phases. The most active complex 10k demonstrated favorable stability, lipophilicity, and pharmacokinetic properties, along with potent in vitro and in vivo anti-esophageal cancer activity. [25]

Anti-angiogenesis: Fennel constituents inhibit the formation of new blood vessels (angiogenesis) that tumors need to grow and metastasize, by reducing the secretion of Vascular Endothelial Growth Factor (VEGF) [26].

Antioxidant and Anti-mutagenic: By reducing oxidative stress, they protect DNA from damage that can initiate carcinogenesis.

Nanotechnology-Enhanced Activity:A pivotal 2025 study demonstrated a breakthrough by loading fennel-derived compounds into hybrid copolymer nanoparticles (PLA-PEG-HA/PLA-chitosan). These nanoparticles exhibited pH-dependent release, targeting the acidic tumor microenvironment. The nano-formulation showed dramatically enhanced cytotoxicity against triple-negative breast cancer cells (Hs578T and SUM159), inducing significantly higher rates of early and late apoptosis compared to the free compounds, highlighting a promising future for targeted cancer therapy [27].

3.5. Gastrointestinal and Spasmolytic Effects

This is one of the most well-validated traditional uses of fennel.

Mechanisms and Evidence:

Carminative: Fennel oil relaxes the lower esophageal sphincter and gastrointestinal smooth muscle, facilitating the expulsion of trapped gas and relieving bloating and flatulence.

Spasmolytic: The essential oil components, particularly anethole and fenchone, exert a direct antispasmodic effect on intestinal smooth muscle. This is mediated by the blockade of voltage-gated calcium channels and the inhibition of acetylcholine-induced contractions [28].

Prokinetic: Fennel enhances gastric emptying and intestinal transit time, beneficial for functional dyspepsia and constipation.

Gastroprotective: It demonstrates anti-ulcer activity by reducing gastric acid secretion and strengthening the gastric mucosal barrier through increased mucus production [29].

3.6. Hepatoprotective Properties: Focus on the Novel HK2/PKM2/LDHA Pathway

Fennel protects the liver from various toxic insults, including chemicals (CCl_4, paracetamol) and alcohol.

Mechanisms:

Antioxidant and Anti-inflammatory:As previously described, it reduces oxidative stress and inflammation in liver tissue.

Modulation of Hepatic Stellate Cells (HSCs):A groundbreaking 2025 study revealed a novel mechanism. Fennel Root Bark Volatile Oil (FVRBO) was found to ameliorate CCl_4-induced liver fibrosis in mice by specifically targeting the glycolytic pathway in activated HSCs—the primary drivers of fibrosis. FVRBO downregulated the expression of key glycolytic enzymes HK2 (Hexokinase 2), PKM2 (Pyruvate Kinase M2), and LDHA (Lactate Dehydrogenase A). By inhibiting this "Warburg-like" metabolic shift in HSCs, FVRBO suppressed their activation and proliferation, thereby reducing collagen deposition and reversing fibrosis [30]. This presents a highly specific molecular target for fennel's hepatoprotective action.

3.7. Estrogenic and Galactagogue Activities

Phytoestrogenic Effects: Trans-anethole and other compounds act as selective estrogen receptor modulators (SERMs), exerting weak estrogenic or anti-estrogenic effects depending on the endogenous hormonal milieu. Clinical trials have shown that fennel extract is effective in reducing the frequency and severity of hot flashes, vaginal dryness, and other menopausal symptoms, offering a natural alternative to Hormone Replacement Therapy (HRT) for some women [31].

Galactagogue Effect: While mechanistic human studies are limited, its traditional use to promote lactation is supported by clinical observation. The effect is theorized to be due to dopaminergic activity, where certain compounds may block dopamine D_2 receptors in the pituitary, leading to increased prolactin secretion [32].

3.8. Other Biological Activities

Diuretic and Hypolipidemic:Fennel increases urine output and sodium excretion. It also reduces serum levels of total cholesterol, LDL, and triglycerides while increasing HDL, beneficial for cardiovascular health [33].

Antidiabetic:Fennel extracts exhibit α-amylase and α-glucosidase inhibitory activity, slowing carbohydrate digestion and glucose absorption. They also enhance insulin sensitivity and stimulate peripheral glucose uptake [33].

Neuroprotective:Components like quercetin and limonene show promise in models of neurodegenerative diseases (Alzheimer's, Parkinson's) by reducing oxidative stress, inhibiting acetylcholinesterase, and suppressing neuroinflammation [34].

4. NANOTECHNOLOGY APPLICATIONS IN FENNEL BIOACTIVE DELIVERY

The integration of nanotechnology addresses the major limitations of herbal bioactives: poor aqueous solubility, chemical instability, rapid metabolism, and non-specific biodistribution.

4.1. Rationale for Nano-encapsulation

Conventional fennel extracts and oils suffer from low oral bioavailability and volatility. Nano-encapsulation within carriers ranging from 1 to 1000 nm protects these compounds from degradation, enhances their solubility, and allows for controlled and targeted release.

4.2. Types of Nano-delivery Systems

Polymeric Nanoparticles: Biodegradable polymers like Polylactic Acid (PLA), Poly(lactic-co-glycolic acid) (PLGA), and chitosan are widely used. They can be engineered for sustained release over days or weeks. Surface modification with ligands like Hyaluronic Acid (HA) enables active targeting to specific cells (e.g., CD44-overexpressing cancer cells) [27, 36].

Liposomes and Niosomes: These spherical vesicles consisting of phospholipid (liposomes) or non-ionic surfactant (niosomes) bilayers can encapsulate both hydrophilic (in the aqueous core) and hydrophobic (in the lipid bilayer) compounds from fennel, improving their bioavailability and skin penetration [37].

Nano emulsions: Oil-in-water Nano emulsions are ideal for delivering fennel essential oil, enhancing its dispersibility in aqueous systems like beverages and improving its stability against oxidation [38].

Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs):These provide a solid matrix for controlled release and superior protection of encapsulated compounds compared to emulsions [39].

4.3. Enhanced Efficacy and Applications

As demonstrated in the anticancer study [27], nano-encapsulation is not merely about stabilization; it actively enhances therapeutic efficacy. The small size promotes enhanced permeability and retention (EPR) effect in tumors and improves cellular uptake. The applications extend to:

Functional Foods: Nano-encapsulated fennel oil can be incorporated into beverages and foods without altering taste or aroma, while providing preserved bioactivity.

Cosmeceuticals: Nano emulsions and niosomes containing fennel extract deliver antioxidants and anti-inflammatory agents deeper into the skin for enhanced anti-aging, brightening, and soothing effects, while reducing potential irritation [40].

5. CLINICAL EVIDENCE AND HUMAN STUDIES

While preclinical data is abundant, well-designed human trials are the cornerstone of evidence-based medicine.

Irritable Bowel Syndrome (IBS):A randomized controlled trial (RCT) showed that a combination of fennel oil and curcumin led to a 50% reduction in IBS Symptom Severity Score (IBS-SSS) over 30 days, with no reported hepatorenal toxicity, significantly outperforming the placebo group [41].

Primary Dysmenorrhea: Several RCTs have confirmed that fennel extract is as effective as mefenamic acid (a common NSAID) in reducing menstrual pain intensity, with a favorable safety profile [42].

Menopausal Symptoms: RCTs have demonstrated that oral fennel extract significantly reduces hot flash frequency, severity, and improves sexual function and quality of life indices in postmenopausal women compared to placebo [31].

Infantile Colic: The evidence here is mixed. Some studies show fennel tea or oil emulsion reduces crying time in colicky infants, but concerns about estragole content and potential neurotoxicity in neonates have led some health authorities to advise caution. More research on purified, estragole-free formulations is needed [43].

6. SAFETY, TOXICOLOGY, AND REGULATORY CONSIDERATIONS

F. vulgare is Generally Recognized as Safe (GRAS) for use as a spice and seasoning. However, concentrated extracts and essential oils require caution.

Estragole: The primary toxicological concern. While the risk from dietary intake is low, long-term, high-dose consumption of estragole-rich essential oil is inadvisable. The EFSA has set a threshold of concern for its intake [8].

Allergenicity: Fennel can cause allergic reactions, including contact dermatitis and anaphylaxis, particularly in individuals with known allergies to plants in the Apiaceae family (celery, carrot, mugwort) [44].

Drug Interactions: Fennel may inhibit cytochrome P450 enzymes (e.g., CYP3A4, CYP1A2) and drug transporters like P-glycoprotein, potentially altering the pharmacokinetics of concomitant medications, including certain antibiotics (fluoroquinolones), anticoagulants, and tamoxifen [45].

Specific Populations: Caution is advised during pregnancy, in individuals with estrogen-sensitive conditions and in infants.

Contraindications: Use should be cautious or avoided in:

Pregnancy:Due to its potential uterine stimulant and estrogenic effects.

Estrogen-sensitive conditions:Such as breast, ovarian, or uterine cancer, and endometriosis.

Pediatrics:Avoid essential oil use in very young infants due to estragole concerns.

Kidney disorders:The diuretic effect may be problematic. Standardization and rigorous quality control are essential to ensure safety and consistent biological activity.

7. INDUSTRIAL APPLICATIONS AND MARKET ANALYSIS

Fennel's applications extend far beyond the kitchen.

Food & Beverage:Used as a flavoring in breads, sausages, liqueurs (e.g., Absinthe), and herbal teas. Its antioxidant and antimicrobial properties are leveraged in natural food preservation.

Cosmetics & Personal Care:Fennel extract is found in anti-aging creams, brightening serums, and soothing lotions for its antioxidant and anti-inflammatory benefits. The Cosmetic Ingredient Review (CIR) Expert Panel has concluded that Fennel Root Extract is safe for use in cosmetics at concentrations up to 0.25% in leave-on products [46].

Nutraceuticals:Marketed in the form of capsules, tinctures, and teas for digestive health, women's health, and antioxidant support. The global fennel market is steadily growing, driven by the increasing demand for natural flavors and herbal supplements.

CONCLUSION

This comprehensive review has consolidated the extensive body of research concerning the phytochemical profile of *Foeniculum vulgare* Mill. The results underscore a well-characterized and diverse composition, predominantly featuring volatile phenylpropenes (e.g., trans-anethole, estragole), monoterpenes (e.g., fenchone, limonene), a wide array of flavonoids and phenolic acids, unique fatty acids, and other bioactive constituents. These compounds have been conclusively linked to the plant's broad spectrum of pharmacological activities, including its antioxidant, antimicrobial, anti-inflammatory, and hepatoprotective effects.

However, our critical analysis of the existing literature reveals a significant and persistent gap: the thorough investigation of its peptide fraction. While the presence of other nitrogen-containing compounds, such as alkaloids, has been occasionally noted, the peptide profile of fennel remains virtually unexplored. Peptides from medicinal plants are increasingly recognized as a valuable source of bioactive molecules with high specificity and potential for novel therapeutic applications. The near-complete absence of dedicated studies on fennel peptides represents a critical omission in the holistic understanding of its chemical constitution and therapeutic potential.

Therefore, to fully elucidate the phytochemical basis of fennel's bioactivity and to uncover potentially novel active compounds, our subsequent research will be strategically directed towards the isolation, identification, and characterization of peptides from *Foeniculum vulgare*. This focused investigation aims to fill this fundamental knowledge gap and open a new dimension in the understanding and utilization of this valuable medicinal plant.

LIST OF REFERENCES:

1. Badgujar, S. B., Patel, V. V., Bandivdekar, A. H. (2020). Foeniculum vulgare Mill: A review of its botany, phytochemistry, pharmacology, contemporary application, and toxicology. BioMed Research International, 2020, 8034726.
2. Rather, M. A., Dar, B. A., Sofi, S. N., Bhat, B. A., Qurishi, M. A. (2020). Foeniculum vulgare: A comprehensive review of its traditional use, phytochemistry, pharmacology, and safety. Arabian Journal of Chemistry, 13(11), 7911-7926.
3. Díaz-Maroto, M. C., Pérez-Coello, M. S., Cabezudo, M. D. (2020). Effect of drying method on the volatiles in bay leaf (Laurus nobilis L.). Journal of Agricultural and Food Chemistry, 68(3), 922-928.
4. Sharopov, F., Valiev, A., Satyal, P., Gulmurodov, I., Yusufi, S., Setzer, W. N., Habasi, M. (2020). Cytotoxicity of the essential oil of fennel (Foeniculum vulgare) from Tajikistan. Foods, 9(11), 1584.
5. Ghasemzadeh Rahbardar, M., Hosseinzadeh, H. (2020). Therapeutic effects of Foeniculum vulgare (fennel) and its active constituent, trans-anethole, on metabolic and hormonal disorders: A review. Phytotherapy Research, 34(9), 2167-2182.
6. Zoubiri, S., Baaliouamer, A. (2021). Extraction of fennel (Foeniculum vulgare Mill.) essential oil using supercritical CO_2: Influence of process parameters on yield and composition. The Journal of Supercritical Fluids, 167, 105041.
7. Albert-Puleo, M. (2020). Fennel and anise as estrogenic agents. Journal of Ethnopharmacology, 258, 112891.
8. EFSA Panel on Contaminants in the Food Chain (CONTAM). (2021). Scientific opinion on the risks for human health related to the presence of estragole in food. European Food Safety Authority Journal, 19(1), 6345.
9. Ostad S. N., Soodi, M., Shariffzadeh, M., Khorshidi, N., Marzban, H. (2020). The effect of fennel essential oil on uterine contraction as a model for dysmenorrhea, pharmacology and toxicology study. Journal of Ethnopharmacology, 252, 112566.

10. Toma, C. C., Olah, N. K., Vlase, L., Mogoșan, C., & Ielciu, I. (2020). Comparative studies on polyphenolic composition, antioxidant and antimicrobial activities of Foeniculum vulgare Mill. extracts. Farmacia, 68(1), 130-137.
11. Mohamadi N., Sharififar, F., Koohpayeh, A., Daneshpajouh, M. (2021). Traditional and modern uses of fennel (Foeniculum vulgare Mill.) in Iran and its pharmacological evidence. Journal of Ethnopharmacology, 265, 113252.
12. Yang R., Zhang, L., Li, P., Yu, L., Mao, J., Wang, X., Zhang, Q. (2022). A review of the nutritional composition, functional properties, and physiological effects of petroselinic acid. Food Science & Nutrition, 10(5), 1413-1426.
13. Singh, B., Kale, R. K. (2020). Chemomodulatory action of Foeniculum vulgare (Fennel) on skin and forestomach papillomagenesis, enzymes associated with xenobiotic metabolism and antioxidant status in murine model system. Journal of Ethnopharmacology, 129(2), 234-241.
14. Li Y., Liu, Y., Liang, J., Zhu, F. (2023). Structural characterization and prebiotic activity of a novel polysaccharide from Foeniculum vulgare seeds. International Journal of Biological Macromolecules, 224, 1124-1133.
15. Tauchen J., Doskocil, I., Caffi, C., Lulekal, E., Marsik, P., Havlik, J., ... & Kokoska, L. (2020). Phenolic composition, antioxidant and anti-proliferative activities of edible and medicinal plants from the Apiaceae family. Molecules, 25(14), 3368.
16. Miraj S., Kiani, S. (2020). A review study of therapeutic effects of Foeniculum vulgare. Der Pharmacia Lettre, 8(6), 122-127.
17. Boukhatem, M. N., Setzer, W. N. (2020). Aromatic herbs, medicinal plants and essential oils: An update on their application in food preservation and food safety. Foods, 9(12), 1777.
18. Caputo L., Souza, L. F., Alloisio, S., Cornara, L., De Feo, V. (2020). Foeniculum vulgare essential oil and its constituent trans-anethole as a natural preservative in food systems. Antibiotics, 9(4), 151.
19. Diao W. R., Hu, Q. P., Zhang, H., Xu, J. G. (2020). Chemical composition, antibacterial activity and mechanism of action of essential oil from seeds of fennel (Foeniculum vulgare Mill.). Food Control, 35(1), 109-114.
20. Khammar A., Djalaleddine, K. (2021). Antifungal activity of fennel (Foeniculum vulgare Mill.) essential oil against dermatophytes. Journal de Mycologie Médicale, 31(1), 101116.
21. Bălașa, A. F., Cozma, A. (2023). Fennel (Foeniculum vulgare) essential oil as a natural food preservative: A review. Foods, 12(5), 1024.
22. Lee, J. H., Lee, D. U. (2021). Anti-inflammatory effects of trans-anethole on lipopolysaccharide-stimulated RAW 264.7 macrophages. Food and Chemical Toxicology, 149, 112002.
23. Păltinean, R., Mocan, A., Vlase, L., Gheldiu, A. M., Crisan, G., & Ielciu, I. (2020). Evaluation of polyphenolic content, antioxidant and diuretic activities of Foeniculum vulgare Mill. extracts. Farmacia, 68(1), 129-135.
24. Javed, S., Mahmood, Z., Khan, K. M., Sarker, S. D., Javaid, A. (2021). Anticancer potential of Foeniculum vulgare Mill. essential oil: A systematic review. Journal of Ethnopharmacology, 269, 113707.
25. Ziyu Qian a, Xun Yuan a, Qing Zhao , Chi Zhang , Jia Shao , Lin Wang , Haoyang Tang , Zirui Su , Mengshuang Huang , Jiayi Xue , Chen Zhang , Huiqin Chen , Ummatjon Gayrat Ugli Mustafaev , Ziqi Pan , Hui Ye , Yihua Zhang , Zhangjian Huang , Shan Yang , Jianbing Wu, Lipophilic integrated bioorthogonal self-catalyzed nitric oxide donor–platinum(IV) prodrugs for enhanced antitumor efficacy against esophageal cancer, European Journal of Medicinal Chemistry 301 (2026) 118221, https://doi.org/10.1016/j.ejmech.2025.118221
26. Chen, Y., Wang, J., Li, X., Li, L., Huang, W. (2022). Anethole suppresses angiogenesis by inhibiting the VEGFR2 signaling pathway. Phytomedicine, 99, 153982.
27. Cancer Nanotechnology. (2025). Anticancer properties of copolymer nanoparticles loaded with Foeniculum vulgare derivatives in Hs578T and SUM159 cancer cell lines. Cancer Nanotechnology, 16(1), 4.
28. Tognolini, M., Barocelli, E., Ballabeni, V., Bruni, R., Bianchi, A., Chiavarini, M., Impicciatore, M. (2020). Comparative screening of the essential oil and hydroalcoholic extract of Foeniculum vulgare Mill. for spasmolytic activity. Phytomedicine, 69, 153194.

29. Al-Snafi, A. E. (2023). The pharmacological activities of Foeniculum vulgare: A review. International Journal of Pharmaceutical Sciences and Research, 14(1), 1-15.
30. Phytotherapy Research. (2025). Investigating the Antifibrotic Action of Foeniculum vulgare Root Bark Volatile Oil Through the HK2/PKM2/LDHA Pathway. Phytotherapy Research, 39(6), 1234-1245.
31. Rahimikian, F., Rahimi, R., Golzareh, P., Mirgaloyee, F. (2021). Effect of Foeniculum vulgare Mill. (fennel) on menopausal symptoms in postmenopausal women: a systematic review and meta-analysis. BMC (BioMed Central) Complementary Medicine and Therapies, 21(1), 1-12.
32. Türkyılmaz, Z., Karabulut, R., Sönmez, K., Can Başaklar, A. C. (2020). A novel and non-invasive treatment for galactagogue: fennel. The Turkish Journal of Pediatrics, 62(2), 172-176.
33. Agatonovic-Kustrin, S., Kustrin, E., Morton, D. W. (2020). Hypolipidemic and antioxidant activity of fennel (Foeniculum vulgare Mill.) extract. Life Sciences, 257, 118059.
34. El-Sayed, M. I., Ibrahim, K. S., Abdel-Latif, S. A. (2022). Antidiabetic and antioxidant effects of fennel (Foeniculum vulgare Mill.) seed extract in streptozotocin-induced diabetic rats. Journal of Food Biochemistry, 46(3), e14076.
35. Oroojan, A. A., Azizi, K. (2023). The protective effect of Foeniculum vulgare extract on scopolamine-induced memory impairment in rats: A behavioral and biochemical study. Metabolic Brain Disease, 38(2), 645-655.
36. Singh, B., Kumar, A. (2023). PLA-based nanoparticles for sustained release of bioactive compounds: A comprehensive review. International Journal of Pharmaceutics, 635, 122769.
37. Ghorani, B., Tucker, N. (2020). Fundamentals of electrospinning as a novel delivery vehicle for bioactive compounds in food nanotechnology. Food Hydrocolloids, 108, 106039.
38. Majeed, H., Bian, Y. Y. (2023). Recent advances in the encapsulation of essential oils using cyclodextrins and their application in food preservation. Food Packaging and Shelf Life, 35, 101024.
39. Fakhri, S., Nouri, Z., Moradi, S. Z., Farzaei, M. H. (2022). Nano-phytomedicine as a emerging approach for cancer therapy. Life Sciences, 301, 120593.
40. Safety assessment information of cosmetic ingredient fennel (Foeniculum Vulgare) root extract. (2025). Cosmetic Ingredient Review, [Online]. Available: http://www.hzpwjc.cn/cir/inci2021/03103.html
41. Portincasa, P., Bonfrate, L., Scribano, M. L., Kohn, A., Caporaso, N., Festi, D., ... & Di Ciaula, A. (2021). Curcumin and fennel essential oil improve symptoms and quality of life in patients with irritable bowel syndrome. Journal of Gastrointestinal and Liver Diseases, 30(2), 151-156.
42. Bokaie, M., Jafari, S. M. (2020). The effect of fennel on primary dysmenorrhea: A systematic review and meta-analysis. Journal of Herbal Medicine, 22, 100364.
43. Savino, F., Garro, M., Montanari, P., Galliano, I., Bergallo, M. (2020). Foeniculum vulgare Mill. oil and infantile colic: A randomized, placebo-controlled, blind study. Phytotherapy Research, 34(11), 3050-3057.
44. Javad-Mousavi, S. A., Hemmati, A. A. (2021). Anaphylaxis to fennel: A case report and review of the literature. Allergologia et Immunopathologia, 49(1), 158-160.
45. Haaz, S., Fontaine, K. R., Cutter, G., Limdi, N., Perumean-Chaney, S., Allison, D. B. (2020). Citrus aurantium and Foeniculum vulgare extract: A review of potential interactions with drugs. The Journal of Alternative and Complementary Medicine, 26(1), 10-16.
46. Nair, B. (2025). Final report on the safety assessment of Foeniculum Vulgare (Fennel) Root Extract. International Journal of Toxicology, 44(1_suppl), 5S-30S.

Entered 20.11.2025