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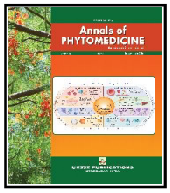

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Fennel (*Foeniculum vulgare* Mill.) in modern phytopharmacology: Bioactive compounds, molecular mechanisms and clinical perspectives

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Abstract

Foeniculum vulgare Mill., commonly known as fennel, is a widely recognized medicinal and aromatic plant with significant phytopharmacological importance. This review comprehensively explores the phytochemical composition, pharmacological activities, molecular mechanisms, clinical relevance and emerging applications of fennel in modern healthcare. Fennel is rich in bioactive compounds, including phenylpropanoids such as trans-anethole, flavonoids, phenolic acids, coumarins and essential oils, which collectively contribute to its diverse therapeutic properties. Extensive pharmacological studies have demonstrated that fennel exhibits a broad spectrum of biological activities, including antioxidant, anti-inflammatory, antimicrobial, anticancer, antidiabetic, neuroprotective, cardioprotective and hepatoprotective effects. These activities are mediated through multiple molecular mechanisms, such as inhibition of inflammatory signaling pathways (*e.g.,* NF-κB), activation of antioxidant defense systems (*e.g.,* Nrf2/ARE pathway), regulation of apoptosis and cell proliferation (PI3K/Akt and MAPK pathways), enzyme inhibition and modulation of gene expression.

Despite its promising pharmacological profile, the clinical application of fennel is limited by challenges related to bioavailability, rapid metabolism and variability in phytochemical composition. Recent advancements in drug delivery systems, including nanoformulations and encapsulation techniques, have shown potential in enhancing the stability, bioavailability and therapeutic efficacy of fennel-derived compounds. Clinical studies have provided evidence supporting its effectiveness in managing digestive disorders, dysmenorrhea and infant colic; however, large-scale, well-designed clinical trials are still required for broader validation. Furthermore, fennel has gained attention in the development of nutraceuticals, functional foods and phytopharmaceutical products, highlighting its role in preventive healthcare. Emerging approaches such as phytonanotechnology, metabolomics and green nanoparticle synthesis are expanding its applications and improving its therapeutic potential. *F. vulgare* represents a promising natural resource with multifaceted pharmacological activities and significant potential for integration into modern medicine. Future research should focus on standardization, molecular validation and clinical translation to fully harness its therapeutic and industrial applications.

1. Introduction

The spice and medicinal species *F. vulgare*, commonly referred to as fennel, has emerged as an important subject of investigation in contemporary phytopharmacology due to its diverse therapeutic attributes and extensive traditional usage. As a member of the Apiaceae family, fennel is widely valued not only as a culinary spice but also as a source of biologically active compounds with significant pharmacological relevance. From a taxonomic standpoint, *F. vulgare* is placed within the order Apiales and represents a monotypic genus, with major variants including bitter fennel (*F. vulgare* subsp. *vulgare*) and sweet fennel (*F. vulgare* subsp. *dulce*), both of which differ in chemical composition and medicinal properties (Rather *et al*., 2021). The plant exhibits characteristic morphological features such as erect, hollow stems, finely divided foliage and yellow umbels, which develop into aromatic fruits rich in volatile and non-volatile phytochemicals (Singh *et al*., 2022). These fruits constitute the principal medicinal component of the plant and are extensively used in both traditional and modern therapeutic formulations. Geographically, fennel is considered to have originated in the Mediterranean region, from where it gradually disseminated to Asia, Europe and other parts of the world through cultivation and trade. In present times, it is cultivated extensively in countries such as India, China, Egypt and Turkey, owing to its adaptability and economic value (Sharma and Tripathi, 2023). Within India, fennel is an important spice crop, particularly in arid and semi-arid regions, where it

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contributes significantly to agricultural income and export potential. The crop performs well in well-drained soils under moderate climatic conditions, although recent agronomic studies indicate that environmental variables such as soil fertility, irrigation regimes and climatic stressors can influence both yield and phytochemical accumulation (Kumar *et al*., 2024). These findings underscore the need for optimized cultivation strategies to ensure consistent quality and enhanced bioactive content.

The long-standing use of fennel in traditional medicinal systems highlights its ethnopharmacological significance. In Ayurvedic medicine, fennel (commonly known as Shatapushpa) is widely used for improving digestion, relieving flatulence and supporting lactation. It is also incorporated into formulations aimed at treating respiratory and gastrointestinal ailments. Similarly, in the Unani system, fennel is regarded as a warming herb with carminative, diuretic and anti-inflammatory properties. In Traditional Chinese Medicine (TCM), fennel is employed to alleviate abdominal discomfort and regulate physiological balance by dispersing internal cold (Ahmad *et al*., 2021). The persistence of these applications across diverse cultural systems suggests a strong empirical basis for its therapeutic efficacy. Recent scientific investigations have substantiated many of these traditional claims, demonstrating that fennel possesses a broad range of biological activities, including antioxidant, antimicrobial, anti-inflammatory and anticancer effects (Khalid *et al*., 2023). The pharmacological potential of fennel is primarily attributed to its rich and diverse phytochemical profile. The plant contains an array of bioactive constituents such as phenylpropanoids, flavonoids, phenolic acids and essential oils. Among these, trans-anethole is recognized as the dominant component of fennel essential oil and plays a central role in its biological activities (Zhao *et al*., 2022). In addition to anethole, compounds such as estragole, fenchone and various polyphenols contribute to the plant's therapeutic properties. Recent studies have demonstrated that these compounds exhibit strong antioxidant capacity by neutralizing reactive oxygen species and enhancing endogenous defense systems (Patel *et al*., 2024). Furthermore, fennel-derived phytochemicals have shown promising results in the management of chronic diseases, including metabolic disorders, cardiovascular conditions and cancer, through mechanisms involving modulation of oxidative stress and inflammatory pathways (Rani *et al*., 2025). Such findings reinforce the importance of fennel as a source of functional bioactive molecules.

In the context of drug discovery, fennel represents a valuable reservoir of natural compounds with significant therapeutic potential. The growing preference for plant-based medicines has intensified research into the identification and characterization of phytochemicals derived from medicinal plants. Compared to synthetic drugs, natural compounds often exhibit lower toxicity and possess the ability to interact with multiple molecular targets, thereby enhancing therapeutic outcomes. This multi-target mode of action is particularly advantageous in the treatment of complex diseases, where single-target interventions may be insufficient (Gupta *et al*., 2022). Advances in analytical methodologies, including chromatographic and spectrometric techniques, have enabled detailed profiling of fennel constituents and facilitated the discovery of novel compounds. Moreover, recent developments in nanotechnology have led to the formulation of nano-based delivery systems for fennel bioactives, improving their stability, bioavailability and therapeutic efficiency (Mehta *et al*., 2023). At the molecular level, fennel-derived compounds have been shown to influence several key biological pathways associated with disease progression. Experimental studies indicate that these compounds can modulate inflammatory responses by suppressing pro-inflammatory mediators and inhibiting enzymes involved in inflammation. Additionally, their antioxidant activity plays a critical role in protecting cellular components from oxidative damage, which is a major contributing factor in the pathogenesis of various chronic diseases (Khalid *et al*., 2023). Emerging evidence also suggests that fennel bioactives can regulate metabolic functions, enhance insulin sensitivity and modulate lipid metabolism, thereby offering potential benefits in the management of metabolic syndrome and related disorders (Rani *et al*., 2025). These mechanistic insights provide a scientific foundation for the therapeutic applications of fennel and support its integration into modern healthcare practices. Despite the promising pharmacological profile of fennel, several limitations must be addressed to facilitate its effective utilization in clinical settings. One of the major challenges is the variability in phytochemical composition, which can arise from differences in geographical origin, cultivation practices and extraction techniques. Such variability can lead to inconsistencies in efficacy and safety, highlighting the need for standardized processing and quality control measures (Kumar *et al*., 2024). Additionally, although numerous preclinical studies have demonstrated the therapeutic potential of fennel, there is a relative scarcity of well-designed clinical trials to confirm these effects in human populations. Concerns regarding the safety of certain constituents, particularly estragole, which may exhibit toxic effects at high doses, also necessitate careful evaluation and regulatory oversight (Zhao *et al*., 2022).

2. Botanical description and ethnopharmacology

The medicinal plant *F. vulgare* is widely recognized not only for its phytochemical richness but also for its distinctive botanical features and extensive ethnopharmacological relevance. A comprehensive understanding of its morphology, traditional nomenclature and cultural significance provides a strong foundation for interpreting its therapeutic applications across different regions and medical systems. Fennel is a perennial or sometimes biennial herb belonging to the Apiaceae family, characterized by its aromatic nature and adaptability to diverse ecological conditions. The plant exhibits an erect, glabrous and branched stem that can reach heights of up to 2-2.5 meters, depending on environmental conditions and cultivar type. Its morphological features are closely associated with its pharmacological value, as different plant parts particularly seeds, leaves and roots contain varying concentrations of bioactive compounds that contribute to its medicinal properties (Rather *et al*., 2021). The leaves of fennel are highly distinctive, consisting of finely dissected, feathery segments that give the plant a soft, delicate appearance. These leaves are arranged alternately along the stem and possess a characteristic aromatic odor due to the presence of volatile oils. The leaf sheath is well-developed, clasping the stem and providing structural support. From a phytochemical perspective, fennel leaves contain flavonoids, phenolic acids and essential oils, which contribute to their antioxidant and antimicrobial properties (Singh *et al*., 2022). In traditional medicine, fennel leaves are often used as mild digestive aids and are incorporated into herbal preparations for their carminative effects. Additionally, fresh leaves are consumed as culinary herbs in various cuisines, further highlighting their functional and nutritional importance.

The reproductive structure of fennel is marked by compound umbels of small, yellow flowers, which are typical of the Apiaceae family.

These flowers eventually develop into dry schizocarpic fruits, commonly referred to as fennel seeds. Botanically, these "seeds" are actually fruits that split into two mericarps upon maturation. The seeds are elongated, slightly curved and greenish to brown in color, with prominent longitudinal ridges. They are the most pharmacologically significant part of the plant due to their high content of essential oils, particularly trans-anethole, fenchone and estragole (Zhao *et al*., 2022). These compounds are responsible for the characteristic sweet aroma and therapeutic properties of fennel seeds. The seeds also contain proteins, carbohydrates and dietary fiber, making them valuable both nutritionally and medicinally. In traditional practices, fennel seeds are widely used as digestive stimulants, breath fresheners and remedies for gastrointestinal discomfort. The root system of fennel is typically composed of a tapering taproot with secondary lateral branches, allowing the plant to anchor firmly in the soil and absorb nutrients efficiently. Although, less commonly utilized compared to seeds and leaves, fennel roots have been reported to contain bioactive compounds with diuretic and detoxifying properties. In certain traditional systems, root extracts are used for managing urinary disorders and promoting metabolic balance (Kumar *et al*., 2024). The structural integrity and physiological functions of the root system also play a role in the biosynthesis and accumulation of secondary metabolites, which can vary depending on soil composition and environmental conditions.

Beyond its botanical characteristics, fennel holds significant cultural and linguistic importance across various regions of the world. It is known by different vernacular names that reflect its widespread use and cultural integration. In India, fennel is commonly referred to as "Saunf" in Hindi, "Perumjeerakam" in Tamil and "Variyali" in Gujarati, indicating its deep-rooted presence in culinary and medicinal traditions. In Arabic-speaking regions, it is known as "Shumar," while in Chinese it is called "Xiao Hui Xiang." These diverse names highlight the plant's global recognition and its incorporation into local healthcare systems (Ahmad *et al*., 2021). The cultural relevance of fennel extends beyond its medicinal uses; it is often associated with rituals, culinary traditions and social practices. For example, in many Indian households, fennel seeds are consumed after meals as a mouth freshener and digestive aid, reflecting a long-standing tradition rooted in Ayurvedic principles. Ethnopharmacologically, fennel has been utilized for centuries to treat a wide range of ailments, particularly those related to the digestive, respiratory and reproductive systems. Its use as a digestive remedy is one of the most well-documented applications across different traditional systems of medicine. Fennel seeds are known to stimulate gastric secretions, enhance appetite and alleviate symptoms such as bloating, flatulence and indigestion. These effects are primarily attributed to the presence of volatile oils that exert carminative and antispasmodic actions on the gastrointestinal tract (Khalid *et al*., 2023). In addition to improving digestion, fennel is also used to manage conditions such as irritable bowel syndrome and gastric ulcers, further demonstrating its therapeutic potential.

In the context of respiratory health, fennel has been traditionally used as an expectorant and bronchodilator. Herbal preparations containing fennel are commonly employed to relieve cough, bronchitis and asthma. The essential oils present in fennel seeds are believed to possess mucolytic properties, which help in loosening and expelling mucus from the respiratory tract (Patel *et al*., 2024). Furthermore, fennel exhibits antimicrobial activity against respiratory pathogens, thereby contributing to its effectiveness in treating infections of the upper respiratory system. These properties have been validated by recent pharmacological studies, which highlight the role of fennel-derived compounds in modulating inflammatory responses and enhancing immune function. Fennel also plays a significant role in reproductive health, particularly in female healthcare. It is widely recognized for its estrogenic activity, which is attributed to compounds such as anethole that mimic the effects of endogenous estrogen. This property makes fennel useful in managing menstrual disorders, including dysmenorrhea and irregular cycles. Additionally, fennel is commonly used as a galactagogue to promote milk production in lactating mothers. Traditional practices in Ayurveda and other systems recommend fennel-based formulations for postpartum care, emphasizing its role in supporting maternal health (Rani *et al*., 2025). Recent studies have further confirmed its potential in alleviating symptoms associated with menopause, such as hot flashes and hormonal imbalances. The ethnobotanical applications of fennel vary across regions, reflecting the influence of cultural practices, environmental conditions and traditional knowledge systems. In Mediterranean countries, fennel is used both as a culinary herb and a medicinal plant, often incorporated into dishes and herbal teas for its digestive benefits. In Middle Eastern cultures, fennel seeds are used in traditional remedies for digestive and respiratory ailments, as well as in spice blends and herbal infusions. In East Asia, particularly in China, fennel is used in Traditional Chinese Medicine to treat abdominal pain, hernia and digestive disorders by regulating the flow of Qi and dispersing internal cold (Ahmad *et al*., 2021). In African traditional medicine, fennel is used for its antimicrobial and anti-inflammatory properties, often as part of polyherbal formulations.

In modern times, the ethnopharmacological significance of fennel has been increasingly supported by scientific research, which has validated many of its traditional uses. Studies conducted between 2020 and 2025 have demonstrated that fennel exhibits a wide range of pharmacological activities, including antioxidant, antimicrobial, anti-inflammatory and anticancer effects (Khalid *et al*., 2023; Patel *et al*., 2024). These findings not only confirm the therapeutic value of fennel but also highlight its potential for integration into evidence-based medicine. Moreover, the growing interest in natural products and plant-based therapeutics has led to renewed attention on ethnobotanical knowledge as a valuable resource for drug discovery. Despite its extensive traditional use, there is a need for systematic documentation and scientific validation of fennel's ethnobotanical applications. Variations in preparation methods, dosage and plant parts used can influence therapeutic outcomes, emphasizing the importance of standardization. Additionally, the preservation of traditional knowledge is crucial in the face of globalization and changing lifestyles, which may lead to the erosion of indigenous practices. Integrating ethnopharmacological knowledge with modern research approaches can provide a holistic understanding of fennel's therapeutic potential and facilitate its development into standardized herbal formulations.

3. Phytochemical composition of *F. vulgare*

The medicinal significance of *F. vulgare* is largely attributed to its rich and diverse phytochemical profile, which encompasses primary metabolites, secondary metabolites and volatile constituents present in its essential oil (Table 1). These compounds are unevenly

distributed across different plant parts, with the highest concentration typically found in the seeds. Advances in modern analytical techniques such as chromatography and spectroscopy have enabled comprehensive identification of these bioactive constituents, revealing their crucial role in the pharmacological potential of fennel (El-Ghorab *et al*., 2021). The phytochemical composition is highly dynamic and influenced by genetic makeup, environmental conditions, agronomic practices and post-harvest handling, all of which significantly impact the quality and therapeutic efficacy of fennel-derived products (Barros *et al*., 2022).

3.1 Primary metabolites

Primary metabolites are fundamental to plant growth and metabolism and also contribute to the nutritional and functional value of fennel. These include carbohydrates, proteins and lipids, which are present in varying amounts depending on plant maturity and environmental conditions. Carbohydrates represent a substantial proportion of fennel seeds and are present mainly as polysaccharides, simple sugars and dietary fibers. These compounds play a vital role in energy metabolism and digestive health. Dietary fibers, in particular, contribute to improved gastrointestinal function by enhancing bowel movement and supporting gut microbiota balance. Recent studies have demonstrated that fennel-derived polysaccharides exhibit prebiotic and immunomodulatory properties, thereby contributing to metabolic health and disease prevention (Al-Snafi, 2020). Additionally, carbohydrate fractions have been shown to possess mild antioxidant properties, further supporting their functional role. Proteins in fennel are present in moderate quantities and consist of a range of essential amino acids that support cellular metabolism and physiological processes. These proteins are involved in enzymatic reactions, structural integrity and metabolic regulation. Recent research has identified bioactive peptides derived from fennel proteins that exhibit antioxidant and antimicrobial activities, indicating their potential application in functional foods and nutraceuticals (Rather *et al*., 2022). The amino acid composition of fennel enhances its nutritional value and supports its inclusion in health-promoting dietary formulations.

Table 1: Major phytochemical constituents of *F. vulgare* and their biological activities

Phytochemical class	Key compounds	Biological activities	Mechanism of action	References
Phenylpropanoids	Trans-anethole, Estragole, Fenchone	Antioxidant, anti-inflammatory, antimicrobial, estrogenic	NF-κB inhibition, cytokine suppression, receptor modulation	Badgujar *et al*., 2021; Brinza *et al*., 2025
Flavonoids	Quercetin, Kaempferol, Rutin	Antioxidant, anticancer, cardioprotective	ROS scavenging, apoptosis induction	Dai and Mumper, 2021; Alam *et al*., 2023
Phenolic acids	Caffeic acid, Chlorogenic acid, Ferulic acid	Antioxidant, antimicrobial	Free radical scavenging, metal chelation	Azmir *et al*., 2021; Khalifa *et al*., 2024
Coumarins	Scopoletin, Umbelliferone	Anticoagulant, antimicrobial	Enzyme inhibition	Badgujar *et al*., 2021
Tannins	Condensed tannins	Antioxidant, antimicrobial	Protein precipitation, microbial inhibition	Alam *et al*., 2023
Sterols	β-sitosterol, Stigmasterol	Cardioprotective, anti-inflammatory	Cholesterol regulation	Kooti *et al*., 2023
Terpenoids	Limonene, α-pinene	Antimicrobial, anti-inflammatory	Membrane disruption	Brinza *et al*., 2025
Fatty acids	Oleic acid, Linoleic acid	Cardioprotective	Lipid metabolism regulation	Badgujar *et al*., 2021

Lipids, although present in smaller quantities, are important due to their composition of essential fatty acids. The lipid fraction of fennel seeds includes fatty acids such as oleic acid, linoleic acid, palmitic acid and petroselinic acid. These fatty acids contribute to membrane stability and play a role in metabolic regulation. The presence of unsaturated fatty acids is particularly important for cardiovascular health, as they are associated with anti-inflammatory and lipid-lowering effects (Badgujar *et al*., 2021). Additionally, these lipids serve as precursors for bioactive molecules involved in cellular signaling pathways, further enhancing their physiological significance.

3.2 Secondary metabolites

Secondary metabolites are the contributors to the pharmacological activities of fennel. These compounds are synthesized as part of the plant's defense mechanisms and include phenylpropanoids, flavonoids, phenolic acids, coumarins, tannins and sterols.

3.2.1 Phenylpropanoids

Phenylpropanoids constitute a major class of bioactive compounds in fennel, with trans-anethole being the dominant constituent. Other important compounds include estragole and fenchone, which contribute to both the aroma and biological activity of fennel. Trans-anethole has been widely studied for its antioxidant, anti-inflammatory, antimicrobial and anticancer properties, making it a key compound responsible for fennel's therapeutic effects (Sharopov *et al*., 2021). Estragole, while biologically active, requires careful evaluation due to its potential toxicity at higher concentrations. Fenchone contributes to the characteristic bitter taste and exhibits antimicrobial and digestive-enhancing properties.

3.2.2 Flavonoids

Flavonoids such as quercetin, kaempferol and their derivatives are abundant in fennel and contribute significantly to its antioxidant capacity. These compounds are known to neutralize reactive oxygen

species and reduce oxidative stress, thereby preventing cellular damage. Flavonoids also modulate various signaling pathways involved in inflammation, apoptosis and immune responses. Recent studies have highlighted their role in reducing the risk of chronic diseases, including cardiovascular disorders and neurodegenerative conditions (Ghasemzadeh and Jaafar, 2021). Additionally, flavonoids contribute to the anti-inflammatory and cytoprotective properties of fennel.

3.2.3 Phenolic Acids

Phenolic acids, including caffeic acid, chlorogenic acid, ferulic acid and p-coumaric acid, are important components of fennel's phytochemical profile. These compounds exhibit strong antioxidant activity by scavenging free radicals and preventing oxidative damage to biomolecules. Phenolic acids also possess antimicrobial and anti-inflammatory properties, making them valuable in disease prevention and management. The concentration of these compounds can vary depending on processing methods such as drying and extraction, as well as environmental factors (Rahimi and Ardekani, 2022). Their presence significantly enhances the overall pharmacological potential of fennel.

3.2.4 Coumarins, tannins and sterols

Fennel contains several minor yet pharmacologically important compounds such as coumarins, tannins and plant sterols. Coumarins are known for their anticoagulant, antimicrobial and anti-inflammatory effects. Tannins exhibit astringent properties and are involved in wound healing and infection control due to their ability to precipitate proteins and inhibit microbial growth. Plant sterols, including β-sitosterol, contribute to cholesterol regulation and cardiovascular health. These compounds collectively enhance the therapeutic profile of fennel and support its use in traditional and modern medicine (Rather *et al*., 2022).

3.3 Essential oil profile

The essential oil of *F. vulgare* is one of the most important components responsible for its characteristic aroma and pharmacological properties. It is typically obtained through hydrodistillation or steam distillation of fennel seeds and consists of a complex mixture of volatile compounds.

3.3.1 Major constituents and composition

The essential oil is predominantly composed of trans-anethole, along with fenchone, estragole, limonene and α-pinene. Trans-anethole is usually the major component, contributing significantly to the oil's biological activity. These compounds are responsible for the antimicrobial, antioxidant and anti-inflammatory properties of fennel essential oil. Variations in the relative proportions of these constituents can influence both the aroma and therapeutic efficacy of the oil (El-Ghorab *et al*., 2021).

3.3.2 Chemotypes and variability

Fennel exhibits distinct chemotypes based on the composition of its essential oil. The two primary chemotypes are the anethole-rich type (sweet fennel) and the fenchone-rich type (bitter fennel). These chemotypic variations arise due to genetic differences and environmental influences, resulting in differences in flavor, aroma and pharmacological activity. Studies have identified multiple chemotypes with varying concentrations of volatile compounds, which can affect the quality and industrial applications of fennel products (Barros *et al*., 2022).

3.3.3 Environmental and genetic influences

The composition of fennel essential oil is significantly affected by environmental factors such as soil type, climate, altitude and agricultural practices. Stress conditions, including drought and nutrient availability, can influence the biosynthesis of secondary metabolites and alter essential oil composition. Genetic variability among fennel cultivars also plays a crucial role in determining essential oil yield and quality. Selection of appropriate genotypes and optimization of cultivation practices are therefore essential for maximizing the production of desired bioactive compounds (Badgujar *et al*., 2021).

4. Extraction, isolation and characterization

The extraction, isolation and characterization of bioactive compounds from *F. vulgare* are fundamental processes in phytochemical and pharmacological research. These steps determine the efficiency of recovery, purity and identification of phytoconstituents responsible for biological activity. The selection of appropriate extraction techniques plays a critical role in preserving the chemical integrity of compounds while maximizing yield. In recent years, there has been a transition from traditional extraction methods toward advanced and environmentally sustainable technologies. Additionally, modern chromatographic and spectroscopic techniques have significantly improved the accuracy of compound identification and standardization, thereby supporting the development of high-quality phytopharmaceutical products (Azmir *et al*., 2021; Chemat *et al*., 2022).

4.1 Conventional extraction techniques

Conventional extraction techniques are widely used due to their simplicity, cost-effectiveness and applicability across different scales. These methods rely primarily on solvent diffusion and solubilization processes to extract phytochemicals from plant matrices. Maceration is one of the most basic extraction methods, involving soaking plant material in a suitable solvent at ambient temperature. This method allows gradual diffusion of bioactive compounds into the solvent and is particularly suitable for heat-sensitive compounds. Infusion and decoction are traditional aqueous extraction techniques widely used in herbal medicine. Infusion involves steeping plant material in hot water, whereas decoction requires boiling for a longer duration to extract compounds from harder plant parts. These methods are especially relevant for fennel, as aqueous preparations are commonly used for digestive and therapeutic purposes (Pandey and Tripathi, 2021). Soxhlet extraction is a continuous extraction technique that enhances efficiency by repeatedly circulating solvent through the plant material. This method is particularly effective for extracting non-volatile compounds such as flavonoids and phenolics. However, prolonged exposure to high temperatures may lead to degradation of thermolabile compounds, which is a limitation of this technique (Azwanida, 2020).

Hydrodistillation is the most widely used technique for extracting essential oils from fennel seeds. In this method, plant material is subjected to boiling and volatile compounds are carried by steam, condensed and collected. This technique is effective for isolating essential oil components such as anethole and fenchone, although it may alter sensitive compounds due to prolonged heating (Chemat *et*

al., 2022). Solvent selection is a critical factor influencing extraction efficiency. Polar solvents such as ethanol, methanol and water are commonly used for extracting phenolic compounds, whereas non-polar solvents such as hexane are used for lipophilic constituents. The polarity of the solvent determines the selectivity and yield of extraction, making solvent optimization an essential step in phytochemical analysis (Azmir *et al*., 2021).

4.2 Advanced and green extraction technologies

The limitations of conventional extraction methods have led to the development of advanced techniques that improve efficiency, reduce processing time and minimize environmental impact. These methods are collectively referred to as green extraction technologies. Ultrasound-assisted extraction (UAE) utilizes ultrasonic waves to generate cavitation effects, which disrupt plant cell walls and enhance the release of intracellular compounds. This technique significantly reduces extraction time and solvent consumption while improving yield and efficiency (Chemat *et al*., 2022). Microwave-assisted extraction (MAE) uses microwave energy to heat the solvent and plant matrix, causing rapid cell rupture and enhanced mass transfer. This method offers high extraction efficiency and reduced processing time, making it suitable for extracting both polar and non-polar compounds (Dai and Mumper, 2021).

Supercritical fluid extraction (SFE) is an advanced technique that uses supercritical carbon dioxide as a solvent. This method is highly efficient and selective, particularly for extracting non-polar compounds such as essential oils. SFE operates under controlled temperature and pressure conditions, preserving thermolabile compounds and producing solvent-free extracts (Pourmortazavi and Hajimirsadeghi, 2021). Enzyme-assisted extraction (EAE) involves the use of enzymes such as cellulases and pectinases to degrade plant cell walls, thereby enhancing the release of bioactive compounds. This method improves extraction efficiency and is particularly useful for recovering phenolic compounds and polysaccharides (Nadar *et al*., 2021). The use of green solvents, including ethanol, water and natural deep eutectic solvents (NADES), has gained attention due to their biodegradability and low toxicity. These solvents provide a sustainable alternative to conventional organic solvents and are increasingly used in eco-friendly extraction processes (Dai and Mumper, 2021).

4.3 Isolation and purification of bioactive compounds

Following extraction, the isolation and purification of individual compounds are essential for structural characterization and biological evaluation. Chromatographic techniques play a central role in achieving high purity and separation efficiency. Column chromatography is a widely used method for separating compounds based on their polarity and interaction with the stationary phase. It involves passing the extract through a column packed with adsorbent material, allowing separation of compounds using solvents of varying polarity (Sasidharan *et al*., 2021). Thin-layer chromatography (TLC) is a rapid and cost-effective technique used for preliminary analysis and identification of phytochemicals. It allows visualization of compounds under ultraviolet light or after chemical staining and is commonly used for monitoring extraction and purification processes (Sherma and Fried, 2020).

Preparative high-performance liquid chromatography (HPLC) is an advanced technique used for isolating pure compounds in larger quantities. It offers high resolution and precise separation, making it suitable for isolating specific bioactive compounds such as flavonoids and phenolic acids (Sasidharan *et al*., 2021). Fractionation strategies involve dividing complex extracts into simpler fractions based on polarity or solubility. Bioassay-guided fractionation is often used to identify fractions with significant biological activity, facilitating the isolation of active compounds responsible for therapeutic effects (Nadar *et al*., 2021).

4.4 Analytical characterization and standardization

Accurate characterization of phytochemicals is essential for determining their structure, composition and biological activity. Modern analytical techniques provide detailed insights into the chemical profile of fennel extracts. Gas chromatography-mass spectrometry (GC-MS) is widely used for analyzing volatile compounds, particularly essential oils. This technique enables identification and quantification of individual components based on their mass spectra and retention times (Azwanida, 2020). High-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS/MS) are commonly used for analyzing non-volatile compounds such as phenolics and flavonoids. These techniques offer high sensitivity, accuracy and reproducibility, making them essential for quantitative analysis (Dai and Mumper, 2021).

Nuclear magnetic resonance (NMR) spectroscopy is a powerful tool for structural elucidation of organic compounds. It provides detailed information about molecular structure and functional groups, enabling precise identification of bioactive constituents (Chemat *et al*., 2022). Fourier-transform infrared spectroscopy (FTIR) and ultraviolet-visible (UV-vis) spectroscopy are widely used for functional group analysis and preliminary characterization. FTIR identifies characteristic absorption bands, while UV-vis spectroscopy is useful for analyzing phenolic compounds and conjugated systems (Sherma and Fried, 2020). Quality control and standardization are critical for ensuring the safety, efficacy and reproducibility of fennel-based products. Standardization involves the use of marker compounds, validation of analytical methods and adherence to regulatory guidelines. These measures ensure consistency in phytochemical composition and support the development of reliable phytopharmaceutical formulations (Pourmortazavi and Hajimirsadeghi, 2021).

5. Pharmacological activities

The pharmacological potential of *F. vulgare* is primarily attributed to its rich repertoire of bioactive phytochemicals, including phenylpropanoids, flavonoids, phenolic acids and essential oil constituents (Table 2). These compounds exert diverse biological effects through multiple molecular pathways, making fennel a promising candidate for therapeutic applications. Recent studies have demonstrated that fennel exhibits significant antioxidant, anti-inflammatory, antimicrobial and anticancer activities, thereby supporting its traditional use and modern pharmacological relevance (Rather *et al*., 2022; Ghasemzadeh *et al*., 2021). The pharmacological actions of fennel are largely mediated by its ability to modulate oxidative stress, inflammation, microbial growth and cellular signaling pathways involved in disease progression.

Table 2: Pharmacological activities of *F. vulgare* with mechanisms and applications

Pharmacological activity	Key bioactive compounds	Mechanism of action	Therapeutic applications	References
Antioxidant	Flavonoids, phenolics	ROS scavenging, Nrf2 activation, SOD/CAT/ GPx enhancement	Oxidative stress-related diseases	Alam *et al*., 2023; Khalifa *et al*., 2024
Anti-inflammatory	Anethole, flavonoids	NF-κB inhibition, cytokine suppression, COX/LOX inhibition	Inflammatory disorders	Habiba *et al*., 2024; Elhady *et al*., 2024
Antimicrobial	Essential oils	Cell membrane disruption	Bacterial and fungal infections	Brinza *et al*., 2025
Anticancer	Flavonoids, phenolics	Apoptosis, PI3K/Akt inhibition, MAPK modulation	Cancer therapy	Benhalima *et al*., 2023; El-Kady *et al*., 2024
Antidiabetic	Phenolics	α-amylase and α-glucosidase inhibition	Diabetes management	Ncube *et al*., 2025
Gastroprotective	Essential oils	Mucosal protection, anti-oxidant effect	Ulcers, indigestion	Rahimi *et al*., 2023
Hepatoprotective	Flavonoids	Reduction of lipid peroxidation	Liver disorders	Barakat *et al*., 2022
Neuroprotective	Flavonoids	Acetylcholinesterase inhibition	Cognitive disorders	Safaei *et al*., 2024
Cardioprotective	Sterols, phenolics	Lipid regulation, antihyper-tensive action	Cardiovascular diseases	Zhou *et al*., 2023
Hormonal/ reproductive	Anethole	Estrogen receptor modulation	Dysmenorrhea, lactation	Kooti *et al*., 2023; Modares *et al*., 2022

5.1 Antioxidant activity

The antioxidant activity of fennel is one of its most extensively studied pharmacological properties. Oxidative stress, caused by an imbalance between reactive oxygen species (ROS) and antioxidant defenses, plays a crucial role in the pathogenesis of various chronic diseases, including cancer, cardiovascular disorders and neurodegenerative conditions. Fennel-derived phytochemicals, particularly flavonoids and phenolic acids, exhibit strong antioxidant potential by scavenging free radicals and enhancing endogenous antioxidant systems. The free radical scavenging mechanism of fennel involves the donation of hydrogen atoms or electrons by phenolic compounds to neutralize reactive species such as superoxide anions, hydroxyl radicals and hydrogen peroxide. Compounds such as quercetin and caffeic acid are particularly effective in stabilizing free radicals due to their hydroxyl group structure. Additionally, fennel extracts have been shown to enhance the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), thereby strengthening the cellular defense system (Shahat *et al*., 2021). Another important mechanism involves the chelation of metal ions, which prevents the formation of highly reactive radicals through Fenton reactions. The presence of polyphenols in fennel contributes to this chelating activity, further reducing oxidative damage. Furthermore, fennel extracts have demonstrated the ability to inhibit lipid peroxidation, thereby protecting cell membranes from oxidative degradation (Badgujar *et al*., 2021). These antioxidant properties not only contribute to disease prevention but also enhance the stability and shelf life of food products when fennel is used as a natural preservative.

5.2 Anti-inflammatory activity

Inflammation is a complex biological response involving immune cells, cytokines and inflammatory mediators. Chronic inflammation is associated with numerous diseases, including arthritis, cardiovascular disorders and cancer. Fennel exhibits potent anti-inflammatory activity through the modulation of cytokine production and inhibition of key inflammatory enzymes. One of the primary mechanisms of fennel's anti-inflammatory action is the suppression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β). Bioactive compounds such as trans-anethole have been shown to downregulate these cytokines, thereby reducing inflammation at the molecular level (Sharopov *et al*., 2021). Additionally, fennel extracts inhibit the activity of cyclooxygenase (COX) and lipoxygenase (LOX), enzymes responsible for the synthesis of pro-inflammatory mediators such as prostaglandins and leukotrienes. Fennel also modulates intracellular signaling pathways associated with inflammation, including the nuclear factor-kappa B (NF-κB) pathway. By inhibiting NF-κB activation, fennel reduces the expression of genes involved in inflammatory responses. Furthermore, its antioxidant properties contribute to anti-inflammatory effects by reducing oxidative stress, which is a key trigger of inflammation (Ghasemzadeh *et al*., 2021). Recent studies have also demonstrated that fennel extracts can

stabilize lysosomal membranes and reduce the release of inflammatory enzymes, thereby protecting tissues from damage. These findings highlight the potential of fennel as a natural anti-inflammatory agent with applications in the management of chronic inflammatory conditions.

5.3 Antimicrobial activity

Fennel exhibits significant antimicrobial activity against a wide range of bacterial and fungal pathogens. This activity is primarily attributed to the presence of essential oil constituents such as anethole, fenchone and limonene, which possess strong antimicrobial properties. These compounds act through multiple mechanisms, including disruption of microbial cell membranes, inhibition of enzyme activity and interference with genetic material. The antibacterial activity of fennel has been demonstrated against both Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus*, *Escherichia coli* and *Salmonella* species. The essential oil components penetrate the lipid bilayer of bacterial cell membranes, leading to increased permeability, leakage of cellular contents and eventual cell death (Rather *et al*., 2022). Additionally, fennel extracts have been shown to inhibit bacterial biofilm formation, which is a major factor contributing to antibiotic resistance. Fennel also exhibits antifungal activity against pathogens such as *Candida albicans* and *Aspergillus* species. The antifungal mechanism involves disruption of cell wall integrity and inhibition of fungal enzyme systems, leading to impaired growth and reproduction. The presence of phenolic compounds further enhances antifungal activity by interfering with fungal metabolism and oxidative processes (Ghasemzadeh *et al*., 2021). The antimicrobial properties of fennel make it a valuable natural preservative in food and pharmaceutical industries. Its ability to inhibit pathogenic microorganisms without causing significant toxicity highlights its potential as an alternative to synthetic antimicrobial agents.

5.4 Anticancer activity

The anticancer potential of fennel has gained significant attention in recent years due to its ability to modulate multiple pathways involved in cancer development and progression. Fennel-derived compounds exhibit cytotoxic effects against various cancer cell lines and have been shown to induce apoptosis, inhibit cell proliferation and arrest the cell cycle. One of the mechanisms of anticancer activity is the induction of apoptosis, a programmed cell death process essential for eliminating damaged or abnormal cells. Fennel compounds such as anethole and flavonoids activate apoptotic pathways by increasing the expression of pro-apoptotic proteins (*e.g.,* Bax) and decreasing anti-apoptotic proteins (*e.g.,* Bcl-2). This leads to mitochondrial dysfunction, activation of caspases and eventual cell death (Zahin *et al*., 2021). Cytotoxic effects of fennel extracts have been observed in various cancer cell lines, including breast, liver and colon cancer cells. These effects are mediated by the generation of reactive oxygen species within cancer cells, which triggers oxidative stress-induced cell death. Additionally, fennel compounds have been shown to inhibit angiogenesis, the process of new blood vessel formation that supports tumor growth. Cell cycle arrest is another important mechanism by which fennel exerts its anticancer effects. Fennel extracts can halt the progression of the cell cycle at specific phases, such as G0/G1 or G2/M, thereby preventing the proliferation of cancer cells. This effect is associated with the regulation of cyclins and cyclin-dependent kinases, which control cell cycle progression (Sharopov *et al*., 2021). Furthermore, fennel exhibits chemopreventive properties by modulating signaling pathways involved in cancer initiation and progression. Its antioxidant and anti-inflammatory activities also contribute to cancer prevention by reducing oxidative damage and chronic inflammation, which are key risk factors for carcinogenesis. These findings suggest that fennel has significant potential as a natural anticancer agent, although further clinical studies are required to validate its efficacy in humans.

5.5 Antidiabetic activity

The antidiabetic potential of *F. vulgare* has attracted significant attention due to its ability to regulate glucose metabolism and improve insulin function. Diabetes mellitus is characterized by chronic hyperglycemia associated with oxidative stress and metabolic dysfunction. Recent studies have demonstrated that fennel exhibits hypoglycemic activity through multiple biochemical mechanisms (Ncube *et al*., 2025). One of the primary mechanisms involves the inhibition of carbohydrate-digesting enzymes such as α-amylase and α-glucosidase, which reduces glucose absorption and prevents postprandial hyperglycemia. In addition, fennel bioactive compounds enhance insulin secretion and improve insulin sensitivity in peripheral tissues. These effects are partly attributed to its antioxidant properties, which protect pancreatic β-cells from oxidative damage and preserve insulin production. Fennel also modulates metabolic pathways by enhancing glycolysis and suppressing gluconeogenesis, thereby improving glucose utilization. Furthermore, its anti-inflammatory activity contributes to improved insulin signaling, making fennel a promising natural agent for diabetes management.

5.6 Gastroprotective and hepatoprotective effects

Fennel exhibits strong gastroprotective and hepatoprotective activities, which are mainly attributed to its antioxidant, anti-inflammatory and cytoprotective properties. It plays an important role in protecting the gastrointestinal tract and liver from chemical and oxidative damage. The gastroprotective effect of fennel is associated with its ability to enhance mucus secretion and strengthen the gastric mucosal barrier. It reduces gastric acid secretion and protects against ulcer formation induced by stress or chemical agents. Additionally, fennel-derived phenolic compounds reduce oxidative damage in gastric tissues, thereby accelerating ulcer healing. The hepatoprotective activity of fennel has been demonstrated in experimental models, where it significantly reduced liver enzyme levels and improved liver histology. Fennel extracts protect hepatocytes from oxidative stress and toxic insults by enhancing antioxidant defenses and reducing lipid peroxidation (Barakat *et al*., 2022). Moreover, fennel promotes detoxification processes and supports bile secretion, which are essential for maintaining liver function. Its anti-inflammatory effects further contribute to reducing hepatic injury and fibrosis, highlighting its therapeutic potential in liver disorders.

5.7 Neuroprotective activity

The neuroprotective properties of fennel have been increasingly recognized due to its ability to modulate oxidative stress, inflammation and neurotransmitter activity. Neurodegenerative diseases such as Alzheimer's disease are often associated with oxidative damage and cholinergic dysfunction. Fennel exerts neuroprotective effects primarily through inhibition of acetylcholinesterase (AChE), an enzyme responsible for the degradation of acetylcholine. By inhibiting

AChE, fennel enhances cholinergic transmission, which is essential for memory and cognitive function. Additionally, fennel contains phenolic and flavonoid compounds that protect neuronal cells from oxidative stress by scavenging reactive oxygen species. These compounds stabilize neuronal membranes and prevent lipid peroxidation, thereby preserving neuronal integrity. Recent studies have also indicated that fennel may reduce neuroinflammation and promote neuronal survival, contributing to improved cognitive performance and memory retention (Barakat *et al*., 2022).

5.8 Cardioprotective effects

Fennel demonstrates significant cardioprotective effects through its ability to regulate lipid metabolism, reduce oxidative stress and improve vascular function. Cardiovascular diseases are closely associated with dyslipidemia, hypertension and inflammation. Fennel has been shown to improve lipid profiles by reducing total cholesterol, low-density lipoprotein (LDL) and triglycerides, while increasing high-density lipoprotein (HDL). These effects are attributed to the presence of phenolic compounds and phytosterols, which regulate cholesterol metabolism and absorption. In addition, fennel exhibits antihypertensive activity by promoting vasodilation and improving endothelial function. It helps relax vascular smooth muscles and regulate ion channels involved in blood pressure control. Fennel also reduces oxidative stress in cardiovascular tissues, thereby preventing lipid oxidation and atherosclerosis. Its anti-inflammatory properties further contribute to cardiovascular protection by reducing vascular inflammation (Zahi *et al*., 2025).

5.9 Hormonal and reproductive effects

Fennel is widely recognized for its hormonal and reproductive health benefits, particularly due to its phytoestrogenic activity. Compounds such as anethole exhibit estrogen-like effects by interacting with estrogen receptors, thereby influencing hormonal balance. This property makes fennel effective in managing menstrual disorders such as dysmenorrhea, irregular cycles and premenstrual syndrome. It helps reduce uterine contractions and alleviate menstrual pain. Fennel is also commonly used as a galactagogue, promoting milk production in lactating mothers. Recent studies have confirmed its effectiveness in enhancing lactation, indicating its potential application in maternal healthcare (Iommelli *et al*., 2025). Furthermore, fennel has been reported to improve reproductive health by reducing oxidative stress in reproductive tissues and supporting hormonal regulation. Its antioxidant activity plays a key role in protecting reproductive cells and improving fertility outcomes.

6. Molecular mechanisms of action

The pharmacological efficacy of *F. vulgare* is mediated through a complex and interconnected network of molecular pathways that regulate inflammation, oxidative stress, apoptosis, metabolism and cellular signaling. The bioactive constituents of fennel, including trans-anethole, flavonoids, phenolic acids and terpenoids, exhibit multi-target interactions that influence intracellular signaling cascades and gene expression patterns. These interactions enable fennel to exert pleiotropic effects, making it a valuable candidate for the management of multifactorial diseases such as cancer, diabetes, cardiovascular disorders and neurodegenerative conditions (Khalifa *et al*., 2024; Rabeh and El-Ghandour, 2023). Recent advances in molecular pharmacology have highlighted that fennel does not act through a single pathway but rather modulates multiple signaling systems simultaneously. This multi-target mechanism enhances its therapeutic potential while reducing the likelihood of resistance commonly associated with single-target drugs.

6.1 Modulation of inflammatory signaling pathways

Inflammation is regulated by intricate signaling networks, with the nuclear factor-kappa B (NF-κB) pathway playing a central role. Fennel-derived compounds have been shown to suppress NF-κB activation, thereby inhibiting the transcription of genes involved in inflammatory responses (Khalifa *et al*., 2024). Normally, NF-κB is sequestered in the cytoplasm by inhibitory proteins (IêB). Upon stimulation by inflammatory signals such as lipopolysaccharides or cytokines, IκB is degraded, allowing NF-κB to translocate into the nucleus. Fennel compounds interfere with this process by stabilizing IκB and preventing NF-κB nuclear translocation, ultimately reducing inflammation. Furthermore, fennel significantly downregulates pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β). These cytokines are key mediators of chronic inflammation and are implicated in various pathological conditions. The suppression of cytokine production by fennel reduces immune cell activation and limits tissue damage (Rabeh and El-Ghandour, 2023). Fennel also inhibits the enzymatic activity of cyclooxygenase (COX) and lipoxygenase (LOX), which are responsible for the synthesis of inflammatory mediators such as prostaglandins and leukotrienes. The inhibition of COX-2, in particular, is associated with reduced inflammation and pain. Additionally, fennel has been shown to modulate Toll-like receptor (TLR) signaling pathways, further contributing to its anti-inflammatory effects. These combined mechanisms position fennel as a potent natural modulator of inflammatory signaling.

6.2 Antioxidant defense and oxidative stress regulation

Oxidative stress results from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, leading to cellular damage. Fennel exerts strong antioxidant effects through both direct and indirect mechanisms, which play a crucial role in its therapeutic activity (Alam *et al*., 2023). The direct antioxidant activity of fennel involves the scavenging of free radicals such as superoxide anions, hydroxyl radicals and peroxyl radicals. Phenolic compounds and flavonoids present in fennel donate electrons or hydrogen atoms to neutralize these reactive species, thereby preventing oxidative damage to lipids, proteins and DNA. In addition to direct scavenging, fennel enhances endogenous antioxidant defense systems by upregulating enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). These enzymes play a critical role in detoxifying reactive species and maintaining cellular redox balance (Khalifa *et al*., 2024). A central mechanism underlying fennel's antioxidant activity is the activation of the Nrf2/ARE signaling pathway. Nrf2 is a transcription factor that regulates the expression of antioxidant and cytoprotective genes. Fennel compounds promote the dissociation of Nrf2 from its inhibitor Keap1, allowing its translocation into the nucleus, where it binds to antioxidant response elements (ARE) and activates gene expression. This leads to increased production of detoxifying enzymes and enhanced cellular protection against oxidative stress (Alam *et al*., 2023).

6.3 Regulation of cell survival, apoptosis and proliferation

The regulation of cell survival and apoptosis is essential for maintaining cellular homeostasis and preventing disease progression.

Fennel influences these processes through modulation of key signaling pathways, including PI3K/Akt and MAPK pathways (El-Kady *et al*., 2024). The PI3K/Akt pathway promotes cell survival and proliferation by inhibiting apoptotic processes. Fennel-derived compounds inhibit Akt phosphorylation, thereby suppressing survival signals and promoting apoptosis in abnormal cells. This effect is particularly significant in cancer cells, where uncontrolled proliferation is a hallmark feature. The MAPK pathway, comprising ERK, JNK and p38 kinases, regulates cellular responses to stress and growth signals. Fennel modulates this pathway by inhibiting ERK activation, which is associated with cell proliferation, while activating JNK and p38 pathways, which promote apoptosis. This dual modulation helps restore cellular balance and prevent uncontrolled cell growth (El-Kady *et al*., 2024). Fennel also induces apoptosis through mitochondrial pathways involving caspase activation. It increases the expression of pro-apoptotic proteins such as Bax and decreases anti-apoptotic proteins such as Bcl-2, leading to mitochondrial membrane disruption and release of cytochrome c. This triggers the activation of caspases, which execute programmed cell death. Additionally, fennel regulates the cell cycle by modulating cyclins and cyclin-dependent kinases, resulting in cell cycle arrest at specific phases such as G0/G1 or G2/M. This prevents the proliferation of damaged or cancerous cells and contributes to its anticancer activity.

6.4 Enzyme inhibition and metabolic modulation

Fennel plays a significant role in metabolic regulation through the inhibition of key enzymes involved in carbohydrate, lipid and neurotransmitter metabolism. These mechanisms contribute to its therapeutic effects in metabolic and neurological disorders (Alam *et al*., 2023). Fennel inhibits α-amylase and α-glucosidase enzymes, which are responsible for carbohydrate digestion. This inhibition reduces glucose absorption and helps maintain blood glucose levels, making fennel beneficial in diabetes management. In addition, fennel inhibits acetylcholinesterase (AChE), an enzyme that breaks down acetylcholine. By inhibiting AChE, fennel enhances cholinergic transmission, which is essential for cognitive function and memory. This mechanism supports its neuroprotective effects. Fennel also modulates lipid metabolism by influencing enzymes involved in cholesterol synthesis and fatty acid oxidation. It reduces lipid accumulation and enhances lipid breakdown, thereby improving lipid profiles and reducing cardiovascular risk.

6.5 Interaction with receptors and ion channels

Fennel bioactive compounds interact with various receptors and ion channels, influencing multiple physiological processes. One of the key mechanisms involves interaction with estrogen receptors, where fennel exhibits phytoestrogenic activity. Compounds such as anethole mimic the action of estrogen by binding to estrogen receptors, thereby regulating hormonal balance and reproductive functions (Rabeh and El-Ghandour, 2023). Fennel also modulates transient receptor potential (TRP) channels, particularly TRPV1, which are involved in pain perception and inflammatory responses. The modulation of these channels contributes to the analgesic and anti-inflammatory effects of fennel. Additionally, fennel interacts with neurotransmitter receptors, including cholinergic and GABAergic systems, which play a role in cognitive function and neuronal signaling. These interactions contribute to its neuroprotective and anxiolytic effects.

6.6 Gene expression and epigenetic regulation

Fennel influences gene expression through modulation of transcription factors and epigenetic mechanisms. It regulates transcription factors such as NF-κB and Nrf2, which control genes involved in inflammation, oxidative stress and apoptosis (El-Kady *et al*., 2024). Epigenetic modifications, including DNA methylation and histone modification, are also affected by fennel compounds. These modifications alter gene expression without changing the DNA sequence and play a crucial role in disease development. Fennel has been shown to modulate epigenetic markers associated with metabolic and inflammatory pathways, thereby influencing disease progression. Furthermore, fennel regulates signal transduction pathways that control cellular responses to external stimuli. By modulating these pathways, fennel enhances cellular adaptability and resilience, contributing to its protective effects.

7. Pharmacokinetics and bioavailability

Understanding the pharmacokinetic behavior of bioactive compounds from *F. vulgare* is essential for translating its pharmacological potential into clinical applications. The therapeutic efficacy of fennel is influenced not only by its phytochemical composition but also by the absorption, distribution, metabolism and excretion (ADME) of its active constituents, particularly trans-anethole, flavonoids and phenolic acids. Recent studies have emphasized that although fennel contains potent bioactive compounds, their clinical effectiveness is often limited by poor bioavailability and rapid metabolism (Dey *et al*., 2023; Singh and Sharma, 2024).

7.1 ADME of key phytochemicals

The absorption of fennel phytochemicals primarily occurs in the gastrointestinal tract. Lipophilic compounds such as trans-anethole are readily absorbed through passive diffusion, whereas hydrophilic compounds such as flavonoid glycosides require enzymatic hydrolysis before absorption. Once absorbed, these compounds are transported *via* the bloodstream to various tissues, where they exert their biological effects. Distribution of fennel-derived compounds is influenced by their chemical structure and polarity. Lipophilic constituents tend to accumulate in fatty tissues and cell membranes, while hydrophilic compounds remain in circulation or are rapidly excreted. Some compounds can cross the blood–brain barrier, contributing to the neuroprotective effects of fennel (Zhou *et al*., 2023). Metabolism of fennel phytochemicals occurs mainly in the liver, where they undergo phase I (oxidation, reduction) and phase II (conjugation) reactions. Trans-anethole, for example, is metabolized into various derivatives that may retain or modify biological activity. These metabolic transformations influence both efficacy and safety. Excretion occurs primarily through urine and bile. Rapid elimination of certain compounds can reduce their therapeutic duration, which is a key limitation in the clinical application of fennel.

7.2 Bioavailability challenges

Despite its pharmacological potential, fennel faces several challenges related to bioavailability. Many of its bioactive compounds exhibit low aqueous solubility, poor stability and rapid metabolism, which limit their absorption and systemic availability. Flavonoids and phenolic compounds often undergo extensive first-pass metabolism, resulting in reduced bioactive concentrations in circulation. Additionally, interactions with intestinal microbiota can further

influence their absorption and transformation. Another challenge is the degradation of thermolabile compounds during processing and storage, which can reduce their effectiveness. Variability in phytochemical composition due to environmental and genetic factors also contributes to inconsistent bioavailability (Singh and Sharma, 2024). These limitations highlight the need for advanced delivery systems to improve the pharmacokinetic profile of fennel-derived compounds.

7.3 Delivery strategies

To overcome bioavailability challenges, modern research has focused on developing advanced delivery systems such as nanoformulations and encapsulation techniques. These approaches enhance solubility, stability and targeted delivery of bioactive compounds. Nanoformulations, including nanoparticles, nanoemulsions and liposomes, have been shown to improve the bioavailability of fennel essential oil and its active constituents. These systems increase surface area, enhance absorption and protect compounds from degradation. For example, nanoemulsions of fennel oil have demonstrated improved antimicrobial and antioxidant activity compared to conventional extracts (Patel *et al*., 2023). Encapsulation techniques, such as microencapsulation and polymer-based delivery systems, are also widely used to protect sensitive phytochemicals and control their release. Encapsulation improves stability during storage and allows for sustained release of active compounds, thereby enhancing therapeutic efficacy. Additionally, the use of biodegradable carriers and green nanotechnology approaches aligns with the growing demand for sustainable and safe drug delivery systems. These strategies are expected to play a crucial role in the development of fennel-based pharmaceuticals and nutraceuticals.

8. Applications in nutraceuticals and functional foods

The incorporation of *F. vulgare* into nutraceuticals and functional foods has gained considerable attention due to its rich phytochemical composition and broad pharmacological profile. Fennel is widely utilized as a dietary ingredient, herbal remedy and functional additive, offering both nutritional and therapeutic benefits. Its bioactive compounds, including phenylpropanoids, flavonoids and essential oils, contribute to health promotion and disease prevention, making it an important component in the development of functional food products (Verma *et al*., 2023; Hassan *et al*., 2024).

8.1 Dietary supplements

Fennel is commonly formulated into dietary supplements such as capsules, tablets, powders and essential oil preparations. These supplements are primarily used to support digestive health, improve metabolic function and enhance overall well-being. The presence of antioxidants and bioactive compounds in fennel contributes to its role in reducing oxidative stress and promoting cellular health. Fennel-based supplements are also used for managing conditions such as bloating, indigestion and mild gastrointestinal discomfort. In addition, its phytoestrogenic properties make it beneficial in women's health, particularly for managing menstrual disorders and supporting lactation. The increasing demand for plant-based supplements has further driven the commercialization of fennel as a nutraceutical ingredient.

8.2 Herbal formulations

Fennel is widely used in traditional and modern herbal formulations, either as a single ingredient or in combination with other medicinal plants. It is commonly included in polyherbal formulations designed for digestive, respiratory and reproductive health. In herbal medicine, fennel is often combined with herbs such as ginger, cumin and coriander to enhance its therapeutic effects. These formulations are used as carminatives, antispasmodics and digestive tonics. The synergistic interactions between fennel and other herbs improve efficacy and broaden the spectrum of pharmacological activity (Hassan *et al*., 2024). Fennel is also used in herbal teas, syrups and extracts, which are widely consumed for their soothing and therapeutic effects. These formulations are particularly popular in traditional healthcare systems and are increasingly being incorporated into modern phytopharmaceutical products.

8.3 Preventive healthcare applications

Fennel plays a significant role in preventive healthcare due to its antioxidant, anti-inflammatory and antimicrobial properties. Regular consumption of fennel or fennel-based products can help reduce the risk of chronic diseases such as cardiovascular disorders, diabetes and cancer. Its antioxidant activity helps neutralize free radicals and prevent oxidative damage, which is a major contributor to disease development. Additionally, fennel supports digestive health, enhances immune function and promotes metabolic balance. Fennel is also used in functional foods such as fortified beverages, bakery products and dietary formulations, where it serves as both a flavoring agent and a health-promoting ingredient. These applications highlight its potential in the development of functional foods aimed at improving public health and nutrition (Verma *et al*., 2023).

9. Emerging trends and advanced approaches

Recent advancements in phytopharmacology and biotechnology have opened new avenues for the utilization of fennel in innovative applications. These emerging approaches focus on enhancing the bioavailability, efficacy and sustainability of fennel-derived compounds.

9.1 Phytonanotechnology

Phytonanotechnology involves the use of plant-derived compounds for the synthesis and delivery of nanoparticles. Fennel extracts have been used in the green synthesis of nanoparticles due to their reducing and stabilizing properties. These nanoparticles exhibit enhanced biological activities, including antimicrobial, antioxidant and anticancer effects (Kumar *et al*., 2024). Nanoformulations of fennel bioactive compounds improve solubility, stability and targeted delivery, thereby enhancing therapeutic efficacy. For example, fennel-based nanoemulsions and nanoparticles have shown improved bioavailability and controlled release of active compounds.

9.2 Synergistic herbal combinations

The use of fennel in combination with other medicinal plants has gained attention due to synergistic effects that enhance therapeutic outcomes. Polyherbal formulations combine multiple bioactive compounds, resulting in improved efficacy and reduced toxicity. Fennel is often combined with herbs such as turmeric, ginger and fenugreek to enhance its pharmacological effects. These combinations are particularly effective in managing complex conditions such as metabolic disorders and inflammation. The concept of synergy is increasingly being explored in modern phytopharmacology to develop more effective herbal therapies (Sharma *et al*., 2023).

9.3 Metabolomics and systems biology

Metabolomics and systems biology approaches are being used to study the comprehensive metabolic profile of fennel and its biological effects. These techniques enable the identification of bioactive compounds and their interactions within biological systems. Metabolomics provides insights into the metabolic pathways influenced by fennel, while systems biology integrates data from genomics, proteomics and metabolomics to understand its overall impact on cellular functions. These approaches help in identifying molecular targets and optimizing the therapeutic use of fennel (Khan *et al*., 2024).

9.4 Green nanoparticle synthesis

Fennel extracts are increasingly used in the eco-friendly synthesis of nanoparticles, offering a sustainable alternative to conventional chemical methods. The phytochemicals present in fennel act as reducing and stabilizing agents, enabling the formation of nanoparticles without the use of toxic chemicals. Green-synthesized nanoparticles using fennel have shown promising applications in drug delivery, antimicrobial therapy and cancer treatment. These nanoparticles exhibit enhanced biological activity and reduced toxicity, making them suitable for biomedical applications (Kumar *et al*., 2024).

10. Future perspectives

Despite the extensive pharmacological potential of fennel, several challenges and opportunities remain in its development as a therapeutic agent. Addressing these issues is essential for advancing its application in modern medicine. One of the major challenges in fennel research is the lack of standardization in phytochemical composition. Variability in environmental conditions, cultivation practices and extraction methods can lead to differences in bioactive compound content. Standardization of fennel extracts is essential to ensure consistency, quality and reproducibility of therapeutic effects. This requires the identification of marker compounds, validation of analytical methods and adherence to regulatory guidelines. Although, numerous preclinical studies have demonstrated the therapeutic potential of fennel, there is a lack of large-scale, well-designed clinical trials to validate these findings. Most clinical studies have small sample sizes and short durations, limiting their applicability. Conducting randomized controlled trials with standardized formulations is essential to establish the efficacy and safety of fennel in human populations. While significant progress has been made in understanding the pharmacological effects of fennel, further research is needed to elucidate its molecular mechanisms. Advanced techniques such as genomics, proteomics and metabolomics can provide deeper insights into its mode of action. Molecular validation is crucial for identifying specific targets and optimizing the therapeutic potential of fennel-derived compounds. Fennel represents a promising source of bioactive compounds for drug development. Its diverse phytochemical profile and multi-target mechanisms make it suitable for the development of novel therapeutic agents. Advancements in nanotechnology, formulation science and molecular biology offer new opportunities for the development of fennel-based drugs. Future research should focus on isolating active compounds, improving bioavailability and conducting clinical trials to translate its potential into practical applications.

11. Conclusion

F. vulgare represents a highly valuable medicinal plant characterized by remarkable phytochemical diversity and broad pharmacological potential. Its rich composition of phenylpropanoids, flavonoids, phenolic acids and essential oils underpin a wide spectrum of biological activities, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, neuroprotective and cardioprotective effects. These properties highlight fennel as a multifunctional therapeutic agent with significant relevance in modern phytopharmacology. The integration of traditional knowledge with contemporary scientific research has played a crucial role in validating the therapeutic uses of fennel. Long-standing applications in systems such as Ayurveda, Unani and Traditional Chinese Medicine are now supported by molecular and pharmacological evidence, demonstrating the importance of ethnopharmacological insights in drug discovery. Advances in analytical techniques, molecular biology and nanotechnology have further enhanced the understanding of fennel's bioactive compounds and their mechanisms of action. Looking ahead, fennel holds strong promise for future therapeutic and industrial applications. Its incorporation into nutraceuticals, functional foods and phytopharmaceutical products offers opportunities for preventive healthcare and disease management. However, challenges such as standardization, bioavailability and limited clinical validation must be addressed to fully realize its potential. Future research should focus on large-scale clinical trials, molecular validation and the development of advanced delivery systems to enhance efficacy and safety.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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