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Therapeutic and pharmacological potential of *Foeniculum vulgare* Mill: a review

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ABSTRACT

Introduction: Fennel (*Foeniculum vulgare* Mill) is one of the oldest spice plants which, due to its economic importance and significant pharmaceutical industry applications, is considered as one of the world's most important medicinal plants. The purpose of this study is to investigate and collect scientific reports such as morphological characteristics, phytochemical compounds and evaluation of the therapeutic properties of this valuable medicinal plant that have been published.
Methods: In order to gather the information the keywords Fennel and Foeniculum vulgare mill, therapeutic, and pharmacology have been searched until January 1, 2015 from journals accessible in databases such as ScienceDirect, Scopus, EBSCO, Medline, PubMed, Embase, SID and Iran Medex.
Results: The results showed that this plant has various pharmacological properties including antioxidant, anti-cancer activity, anti-inflammatory, antifungal, anti-bacterial and estrogenic effects which are probably due to the presence of aromatic compounds such as anethole, estragole and fenshon.
Conclusion: Fennel possesses various pharmacological properties and the fennel bioactive molecules play an important role in human health, hence, it might be used for different drug productions.

Implication for health policy/practice/research/medical education:
Fennel (*Foeniculum vulgare* Mill) has different pharmacological properties such as anti-allergic, analgesic, anti- inflammatory, antioxidant, antibacterial, anti-cancer, anti-stress, cytotoxicity, etc. The fennel bioactive molecules play an important role in human health and can be used for different drug productions.
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Introduction

The use of herbs to treat diseases has been common since ancient times. Also the use of plants different parts is common in public health. Using natural remedies and herbal medicines is beneficial cost-effective method for treating diseases (1,2).

Nowadays medicinal herbs are good alternative to chemical drugs, one of the major reason for this is low side effect compared to chemical drugs (3,4). Plants have always played an important role in the health and treatment of human society (5). Medicinal herbs have fewer side effects than synthetic drugs and due to their antioxidant properties they reduce drugs toxicity (6,7). Also, the natural effective ingredients cause biological balance and prevent drug accumulation in body (8). So medicinal plants can be used in the treatment of various diseases (9)

From 422 000 flowering plants around the world, more than 5000 ones are used for medicinal purposes. Among these herbs can point to fennel (*Foeniculum vulgare* Mill) which is of great importance and is used in the pharmaceutical, food, cosmetic and healthcare industries (10). Fennel is one of the oldest spice plants which widely grows in arid and semi-arid and due to its economic

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importance and pharmaceutical industry usage, it is one of the world's most dimension medicinal herb (11). This plant has anti-inflammatory, antispasmodic, antiseptic, carminative, diuretic and analgesic effect and is effective in gastrointestinal disorder treatment. Also with its anti-ulcer and anti-oxidant properties it is used to treat neurological disorders (12,13). According to importance of fennel as a medicinal herb, the aim of the present study was to evaluate the phytochemical characteristics, and therapeutic properties of this medicinal plant.

Methods

In order to gather the information the keywords Fennel and *Foeniculum vulgare* mill, therapeutic, and pharmacology have been searched until January 1, 2015 from journals accessible in databases such as ScienceDirect, Scopus, EBSCO, Medline, PubMed, Embase, SID and Iran Medex.

Results

Phytology

Foeniculum vulgare Mill with English name of Fennel, Fenouil in French, Shmr (Razianaj) in Arabic and Razianeh in Persian belongs to Apiaceae family. It is an herbaceous and aromatic plant, with a height of 1 to 2 meters, grows in many parts of Europe, the Mediterranean, and Asia. Fennel is a perennial herb with stems grooved, intermittent leaves, often combined with dark green, fluffy with a blade divided into thin pieces, petiole with sheath, flowers are usually bisexual, regular or irregular, with yellow umbrella in the form of oval beads (14,15). On radiating branches linear lines can be diagnosed. Fennel has small seed with a length of about 8 mm and a width of 3 mm with an aromatic odor and sweet taste. Fennel seeds are narrow, long, cylindrical appearance and dimensions vary depending on plant growth. The crack groove light green surface (16).

Phytochemical composition of fennel

All parts of fennel such as roots, leaves, fruit and especially the seeds are used (17). Fennel seed contains 6.3% water, 9.5% protein, 10% fat, 13.4% minerals, 18.5% fibers and 42.3% carbohydrates (18). Its leaves contain vitamins and minerals such as calcium, potassium, sodium, iron, phosphorus, thiamine, riboflavin, niacin and vitamin C (19). Fruits consist 10 to 12 % of oil that is stored in the cotyledons of seeds. Oil obtained from the fennel fruit has 4% palmitic acid, 22% oleic acid, 14% linoleic acid and 6% petrocylic acid. The fruit has value of 4 to 6% essence which its essence and combine ingredients vary according to the location of plant growth (16). The aromatic property of fennel is because of the essence. There are more than 30 types of terpene compounds in the essential oil of fennel, the most important of them are 50 to 80% trans-anethole, 8% fenshon and limonene 5% (20). This herb also contains phenolic compounds such as flavonoids, phenolic acids, hydroxycinnamic acids, coumarin and tannin (21). Phenolic acids include 3-O-Caffeoylquinic acid, 4-O-caffeoylquinic acid, 5-O-caffeoylquinic acid, 1, 3-O-di-caffeoylquinic acid, 1, 4-O-di-caffeoylquinic acid and 1, 5-O-di-caffeoylquinicacid. Its flavonoid contains eriodictyol-7-rutinoside, quercetin-3-rutinoside and rosmarinic acid (22). Also aqueous extract of fennel fruit include quercetin-3-O-galactoside, kaempferol-3-O-rutinoside, kaempferol-3-O-glucoside, quercetin-3-O-glucuronide, kampferol-3-O-glucuronide, isoquercetin, and isorhamnetin-3-O-glucoside (23).

Use of fennel in traditional medicine

Fennel has been used in traditional medicine to treat various diseases for thousands of years in the East Asian countries, India and China (16). People have long been familiar with fennel plant. In the middle ages people believed that chewing the seeds is important to eliminate abdomen noise (24). In the fifth century it was believed that fennel had sedative effect and in 9th to 14th centuries numerous therapeutic properties were attributed to it (25). The Romans believed that fennel seed could help supercharge the vision. The English believed that the plant could offer relief from bloating stomach and facilitate digestion. The fennel therapeutic use has been serious since the 18th century, and many studies have been taken (26). Nowadays, the different parts of the plant are used in treatment of many diseases, particularly pain in the digestive system. Also it is very useful in the treatment of diabetes, bronchitis, chronic cough and kidney stones (27). Fennel seeds are used as a flavoring in cooking meat and fish, prepare ice cream and cream. Due to its diuretic effect the plant is used to treat kidney and bladder diseases. It is also used to relieve nausea and remove vomiting. The herbs is helpful for chronic fever and removing the obstruction in the internal organs, especially the liver, gut, respiratory and urinary tract and also it is used to improve eye diseases such as cataract as well as diseases of the stomach, chronic diarrhea and relieve children colic (28,29).

Pharmacological effects

The pharmacological activities of fennel include following items (30).

Anti-bacterial activity

Fennel is used to treat many bacterial, fungal, viral, and mycobacterial infectious diseases (31). Fennel has antibacterial activity due to compounds such as, linoleic acid, undecanal, 1, 3-benzenediol, oleic acid and 2,4-undecadienal. Fennel has 5-hydroxy-furanocoumarin which has important role antibacterial activity of this plant (32). Aqueous extract of fennel shows bactericidal activity against Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi, Salmonella typhimurium, and Shigella flexneri (33). During a study it was found that this plant extract has a significant antibacterial effect against a lot of bacteria except Klebsiella pneumoniae and one strain of Pseudomonas aeruginosa. Also this report determined MIC for aqueous

and alcoholic extracts of fennel seed which was in the range of 20-80 mg/ml and 5-15 mg/ml and statistical analysis showed better effect of the plant extract compared to standard antibiotics (34). The essence of plant showed very strong antibacterial activity against pathogens in food such as Escherichia coli, Listeria, monocytogenes, Salmonella typhimurium, Staphylococcus aureus, as well as having enormous activity against Helicobacter pylori and Campylobacter jejuni (35,36).

Jazani *et al*. studied the antibacterial activity of fennel extract on Acinetobacter baumannii strains which cause nosocomial infection. The results showed that fennel extract has antibacterial effect on all bacteria strains so its' extract can be used to control multiple-antibiotic resistant bacteria (37).

Anti-fungal activity

Fennel extract has antifungal activity against various fungal species such as Candida albicans, species of Aspergillus, and dermatophytes (21). Also a study on the herb antifungal effect showed significant antifungal activity against fungi in food waste such as Aspergillus niger and Fusarium oxysporum. The MIC of fennel extract for these molds respectively was 750 and 250 micrograms per ml (27).

Another study showed that dillapional the derivative of fennel stalk phenyl propanoid has antimicrobial properties against Aspergillus niger, Bacillus subtilis and Cladosporium cladosporioides. Also derivates of coumarin named scopoletin had antimicrobial properties against above micro-organisms but was less important than dillapional (38).

Antifungal activity of fennel essence on Sclerotinia sclerotiorum was investigated. The antifungal effect of this plant against Sclerotinia sclerotiorum observed based on survival of the microorganisms (39).

A study demonstrated that nitric oxide production in peritoneal macrophages which were treated with fennel extract at a concentration of 10 mg/ml significantly increased. Also the production of reactive oxygen species compared to the control group increased. Lethality study also showed that treated macrophages with concentrations of 10 and 20 mg ml had anti-candidate effects more than control group. Among chemical compositions of the plant extract anethole had the strongest antifungal activity (40).

Antioxidant activity

Fennel is known as an excellent source of natural antioxidants. This plant can inhibit free radicals due to the high content of polyphenols and flavonoids. Phenolic compounds in this herb such as caffeoylquinic acid, rosmarinic acid, eriodictyol-7-orutinoside, quercetin-3-O-galactoside, kaempferol-3-O-glucoside showed antioxidant activity. Fennel volatile oil has strong antioxidant activity, too. Plant ethanolic and aqueous extracts in comparison to its essence has less antioxidant activity (33,41-43).

In a research aqueous and methanolic extracts of fennel seed for Total Antioxidant Capacity (TAC) and determination of total phenolic compounds were studied. TAC was measured using the DPPH, H2O2, and FRAP and phenolic compounds using the Folin-ciocalteu reagent. This study showed that fennel extracts could inhibit free radicals and act as primary antioxidant (41).

In another study, the antioxidant activity of aqueous and ethanol extracts of fennel seeds was evaluated by using a variety of antioxidant methods such as total antioxidant, free radical scavenging, superoxide anion radical scavenging, hydrogen peroxide scavenging, metal chelating activity. These antioxidant activities were compared to standard antioxidant such as butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT), and a-tocopherol. The results obtained in this study showed that fennel seed was a potential source of natural antioxidants (44). Also antioxidant activity of the ethanol and aqueous extracts of fennel showed that 100 mg of ethanol and watery extracts respectively had the 99.1% and 77.5% of antioxidant activity which was greater than the alpha-tocopherol (36.1%) antioxidant properties with the same dose (45).

Anti-inflammatory activity

Of the pharmacological effects of fennel plant, anti-inflammatory activity can be noted. Research has shown that the methanol extract of fennel has anti-inflammatory effects. Oral administration of 200 mg per kg of methanol extract of fennel fruit shows inhibitory effects on acute and subacute inflammatory diseases and type 4 allergic reactions. In addition, it decreased the activities of superoxide dismutase (SOD) and catalase (CAT). It also significantly increased plasma levels of HDL cholesterol. In contrast, it significantly reduced the level of malondialdehyde (MDA) as a measure of lipid peroxidation. These results indicate that the methanol extract of fennel fruit is effective in reducing inflammation (46). Kataoka et al. studied anti-inflammatory effects of fennel. The results showed that the methanol extract of fennel seeds inhibits inflammation through cyclooxygenase and through lipoxygenase pathways (47,48). Also Choi et al. evaluated fennel methanol extract anti-inflammatory effects. The results showed that the fennel methanol extract had anti-inflammatory activity dependent on the central and peripheral mechanisms (46).

Anti-anxiety activity

Anxiolytic activity of the crude extract of fennel has been reported. Fennel due to phytoestrogens extensively has therapeutic use in the treatment of estrogen deficiency abnormalities. Estrogens are hormones that are involved in the phenomenon of anxiety which appear to act via the GABA A receptors. The results of a study showed that the plant with increase in time spent in the open arm established significant anxiolytic effect. Picrotoxin (GABA receptor antagonist) and Tamoxifen prevented anxiolytic effect. Therefore, fennel probably is an herbal remedy that has anxiolytic effects mediated by GABA-ergic system and

estrogen receptors (14).
Mesfin *et al.* studied the anxiolytic activity of fennel on adult mice. It was demonstrated that stress levels in treated group with fennel essence compared to control group significantly decreased. Thus, it can be concluded that this plant can hold promising effects in the treatment of anxiety and stress (49).
Koppula *et al.* investigated the properties of fennel extract in stress reduction and memory enhancement in rats. This study showed that this herb with several functions such as anti-stress proceeding, increase in memory and antioxidant effects may reduce stress and stress-related disorders (50).

Gastro-protective activity

It has been shown that fennel plant has significant protective effect on gastrointestinal disorders. It was shown that the use of fennel oil emulsions eliminated colic in 65% of treated infants which was considerably better than the control group (51,52). In a study Al-Mofleh *et al.* investigated the effect of fennel plant on gastric ulcer. The findings showed that the plant had a protective effect on gastric ulcer. In addition, the herb reduced mucosal lining of the stomach. These functions were attributed to its antioxidant capacity (53).

Estrogenic activity

Fennel has been used for thousands of years as an estrogenic agent. Due to this property, fennel increases milk secretion, reduces menstrual pain, facilitates birth and increases sexual desire. Anatole is the main part of fennel plant that operates estrogenic properties. Researches have shown that active pharmaceutical agents such as dianthole and photoanatole are polymers of anthole (48).
The fennel essence showed fewer side effects in the treatment of primary dysmenorrhea. Administration of different doses of fennel extract significantly decreased contractions intensity induced by oxytocin and prostaglandins (54). Moderate doses increased mammary gland weight and higher doses increased the weight of oviduct, endometrium, myometrium and cervix (55). Myrseyed *et al.* investigated the effect of fennel seed ethanol extract on gonadotropin changes in adult male rats. Testosterone, FSH, LH levels in treatment groups were significantly reduced in comparison to the control group. Significant reduction in the amount of sperm resulting in epididymis weight loss and hormone levels indicates the fennel seed decreases in male reproductive activity (56).
Fennel herb has estrogenic effects and has been traditionally used to treat infertile women. It was shown that the extract of fennel increased serum concentrations of follicle-stimulating hormone and decreased the yolk hormones and testosterone in treatment groups (57). In another study Devi *et al.* investigated fennel fruit acetone extract effect on mammary gland and oviduct. The results of this study confirmed the effects of natural estrogen for this plant seed extract (58).

Cardiovascular and lipid activity

The study of the anti- cholesterol and anti-atherogenic effect of fennel methanol extract showed that treatment with the extract significantly reduced plasma lipid levels. Also the plant had important anti-atherogenic effects. It reduced triglycerides in fatty liver and facilitated blood flow in the coronary arteries by preventing the buildup of fatty deposit in arteries through reduction of plasma and liver fats. As a result because of hypolipidemic and anti-atherogenic activities, this herb could be used for controlling cardiovascular disorders (59,60). Also intravenous injection of the extract significantly reduced blood pressure, without affecting the heart rate and respiration. It seems that fennel extract effect on blood pressure was not mediated by adrenergic, muscarinic, ganglion, serotonergic receptors (61). In other study, oral administration of the extract reduced systolic blood pressure. The fennel extract acts as a diuretic and natriuretic, too (62).

Anti-diabetic activity

A study investigated the effect of aqueous extract Apiaceae family plant such as fennel in lowering blood sugar and anti-diabetic activities. The findings exhibited that the extract could be useful for the control of blood glucose in diabetic patients and in addition, their daily use could be effective in reducing chronic complications associated with diabetes (63).
To evaluate the effect of fennel on blood sugar reduction, a study was conducted on streptozotocin-diabetic rats. The results showed that fennel extract improves hyperglycemia in diabetic rats which part of this related to herb effect on oxidation/restored system. Therefore, this plant can be used in the pharmaceutical industry for the manufacture of anti-diabetic drugs (64). Also methanol extract of fennel fruit reduced blood glucose and triglycerides and led to higher levels of liver and muscle glycogen (65).

Anti-cancer activity

It was shown that TNF-α -dependent responses are involved in inflammation and cancer. It was found that anethole in fennel seed has inhibitory effect on activating TNF-α by transcription factor NF-KB. The results showed that anethole inhibited cellular responses induced by these cytokines which might explain its role in suppressing cancer. It also specified that the fennel with its antiangiogenic mechanisms inhibits prostate tumor xenograft (66).
Bogucka-Kocka *et al.* evaluated apoptotic activity of ethanol extracts of fennel against leukemia. The findings showed that the extract had considerable apoptotic effects on cancer cells (67). In other study, fennel methanol extract effects on antitumor and cytotoxic activities in mice with cancer were investigated. Data of this study showed that the methanol extract of fennel considerably increased MDA levels and significantly reduced CAT activity and glutathione content in the liver and tumor tissue of mice with cancer. In contrast, the total protein content in the

ascites fluid decreased. The results demonstrated that the methanol extract of fennel had significant anticancer activity against breast cancer cells (MCF-7) and liver cancer (Hepg) through modulating lipid peroxidation and increasing antioxidant defense system and inhibitory effect on free radicals (68).

Hepato-protective activity

The studies demonstrated that the fennel plant has protective effect on liver. Qiang *et al.* studied the effect of fennel extract in carbon tetrachloride -induced liver injury rats. Data from this study showed that this extract reduced the levels of AST (aspartate aminotransferase), ALT (alanine amino transferase), ALP (alkaline phosphatase) and serum bilirubin (69). Also the effect of fennel on lipid peroxidation in rats with hepatic fibrosis was investigated. After fennel consumption ALT, AST level and MDA content significantly decreased and the TP, ALB and SOD, CAT, GSH-PX activities increased. According to results it might be concluded that fennel probably through effect on regulation of lipid peroxidation might inhibit hepatic fibrosis (70).

Wang *et al.* studied fennel effect on cytokines in rats with hepatic fibrosis. The results demonstrated that degradation of lipids and inflammation was reduced in the fennel treated group. Based on the data obtained from this study can be deduced that fennel might reduce inflammation in the liver and also considerably protect hepatocytes against liver damage (71). In other study, the effect of fennel on hepatic fibrosis and the amount of potassium supplements examined. Patient group with fibrosis, liver tissue inflammation and excessive fat degradation after fennel treatment significantly improved. After treatment with fennel of ascites level and HAase content decreased and potassium levels went up. According to these findings it can be derived that fennel might inhibit hepatic fibrosis (72). Also, the effect of fennel on TNF-α cytokine in liver fibrosis model was examined. In the treated group inflammation was reduced and the amount of TNF-α secretion was reduced by PBMCS (73). Based on these findings, we can conclude that fennel might reduce TNF-α secretion by single –core cells, inhibit inflammation and improve liver fibrosis.

Memory-protective activity

It is believed that some plants including fennel herbs are used to enhance memory and intelligence. Therefore, the effect of fennel extract on memory in amnesiac rats was examined. The results showed that this extract had memory enhancement property (27). In Joshi *et al.* study the effect of fennel extract as a neurotropic factor and anti-acetylcholinesterase in mice were investigated. The findings of this study showed that fennel extract significantly inhibited acetylcholinesterase. According to this study it can be deduced that fennel might be used in treatment of cognitive disorders such as dementia and Alzheimer (74).

Potential mechanisms

According to the literature, some potential mechanisms of the plant's effects have been shown in Table 1.

Side effects

In general, for preparing herbal products minimal toxicity and minimal side effects are very important. Estragole is one of the most important fennel extract compounds. It is reported that this compound led to the development of malignant tumors in rodents, so use of this agent is restricted (18). The Estragole causes tumors in rodents but carcinogenicity in humans has not been established. The total amount of anethole in fennel is 2090 mg/kg. It has been reported that repeated administration of 695 mg/

Table 1. The potential mechanisms of efficacy of some pharmacologic properties of *Foeniculum vulgare* Mill

Pharmacological effects	Possible mechanisms of efficacy
Anti-microbial activity	Presence of active compounds with anti- microbial activity such as oleic acid and coumarin in aqueous and alcoholic extract.
Antioxidant activity	Presence of antioxidant compounds such as flavonoid and phenols in aqueous and ethanolic extract.
Anti-inflammatory activity	The Preventive effects of methanol extract against acute and subacute illness, type 4 allergic reactions through cyclooxygenase and lipoxygenase inhibition.
Anti-anxiety activity	Anxiolytic effects mediated by GABAergic and estrogen receptors
Gastro-protective activity	Regulation of intestinal muscle movement, treatment of gastrointestinal spasm and chronic colitis, protective effect on gastric ulcer, reduce the mucosal lining of the stomach.
Estrogenic activity	Presence of compounds such as anatole effect on increasing milk secretion reduce menstrual pain, facilitate birth, primary dysmenorrhea, and infertility.
Anti- lipid activity	Hypolipidemic effects by reducing plasma triglyceride, total cholesterol, lowering LDL, decreased apolipoprotein B, increased HDL, and increased apolipoprotein A-1.
Cardiovascular activity	Systolic blood pressure reduction, decreased excretion of sodium, potassium and water.
Anti-diabetic activity	The hypoglycemia effect by lowering blood glucose, increasing glutamine peroxide activity, increased levels of liver and muscle glycogen.
Anti-cancer activity	Presence of active compounds such as anethole, inhibitory effect on the activation of TNF-α, antiangiogenic effects, and apoptotic and antitumor effects.
Hepato-protective activity	Decreased levels of AST, ALT, ALP and Bilirubin, reduction of proinflammatory cytokines such as TNF- α and CTGF in fibrosis.
Memory-protective activity	Inhibitory effect on the acetylcholinesterase enzyme.

kg caused a mild lesions in the rat liver. Thus, it was found that normal therapeutic doses of anatole cause mild liver toxicity (75).

It is reported that the use of fennel extract for control and treatment of primary dysmenorrhea causes concern about the teratogenicity potential of it, due to its estrogen-like activity. Investigating the herb extract effect showed teratogenic property that may have toxic effects on the cells of the embryo but no evidence of teratogenicity to concentration of 9.3 mg/ml (76).

Conclusion

Available researches have shown that extracts of fennel possess different pharmacological properties such as anti-allergic, analgesic, anti-inflammatory, antioxidant, antibacterial, anti-cancer, anti-stress and cytotoxicity activity. Medicinal properties of the plant are due to its different chemical compounds. Among the various compounds found in fennel plant essence and phenolic compounds are considered as the most important and most active compounds of it. The fennel bioactive molecules can be used for different drug production and play an important role in human health. The most prominent and best studies have been conducted on the antioxidant, antimicrobial and fennel estrogenic effects in various experimental models. Few studies have been performed on the anticancer effect of this plant, while a high percentage of worldwide deaths occur as various cancer effects. Therefore, it is recommended that future researches be investigate on the effect of this plant on cancer cell lines.

Authors' contributions

All the authors wrote the manuscript equally.

Conflict of interests

The authors declared no competing interests.

Ethical considerations

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