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Chemical composition, therapeutic potential and perspectives of *Foeniculum vulgare*

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Abstract
Foeniculum vulgare is a widely distributed plant in most tropical and subtropical countries and have long been used in folk medicines to treat obstruction of the liver, spleen and gall bladder and for digestive complaints such as colic, indigestion, nausea and flatulence. In recent years the interest in this plant has increased considerably with substantial progress on its chemical and pharmacological properties. This review discusses the current knowledge of its chemistry, the various compounds isolated and pharamcological studies conducted. These studies carried out with the extracts and volatile oil support most of the reports of using this plant in folk medicines. However, well controlled, double-binding clinical trials are lacking. Several compounds including trans-anethole, estragole, fenchone and polyphenolics were isolated from this plant and some of these interact with potential mechanisms of the body. Together this data strongly supports the view that this plant has potential beneficial therapeutic actions in the management of bacterial and fungal infections, colic pain and lipid peroxidation.
Key words: ***Foeniculum vulgare, volatile oil, antibacterial, antifungal, mosquito repellent, antioxidant.***

Introduction

Natural products, mainly the plant-derived constituents, have long been sources of drugs, and a great part (30–40%) of the pharmaceuticals available in modern medicine is directly or indirectly derived from natural sources. Natural products are also of great interest in the process of drug discovery, due to their large diversity in nature, permitting the identification of lead molecules of greater interest for the development of new therapeutic agents, as well as biochemical and molecular tools needed to clarify complex cellular and molecular mechanisms of action involved in most physiological and pathological processes. Furthermore, a growing world-wide interest in the use of phytopharmaceuticals as complementary or alternative medicine, either to prevent or to ameliorate many diseases, has been noted in recent years. It is believed that about 80% of world's population use plants as their primary source of medicinal agents (1-5).

Foeniculum vulgare (fennel) is a typical aromatic plant of the Mediterranean area, long used as a medicinal and spice herb. Well-known for its essential oil, fennel has been extensively studied for many years owing to its commercial importance. It is a biennial or perennial herb up to 2 meters high, with feathery leaves and golden yellow flowers. There are two main varieties of fennel: bitter or common fennel, slightly taller with less divided leaves occurring in a cultivated or wild form and sweet fennel (also known as Roman, garden or French fennel) which is always cultivated. Bitter fennel is native to the Mediterranean region, found growing wild in France, Spain, Portugal and North Africa. It is cultivated extensively world-wide, the main oil producers being Hungary, Bulgaria, Germany, France, Italy and India. Sweet fennel is thought to have originated on the island of Malta, having been introduced by monks or crusaders thousands of years ago. It is now grown principally in France, Italy and Greece (6-10).

The purpose of this review is to provide a comprehensive update on the status of the recent chemical, pharmacological and future scope of the extract and active constituents isolated and identified in this plant to be used as antibacterial, antifungal, antioxidant, antispasmodic and mosquito repellent.

Chemical constituents isolated from *Foeniculum vulgare*

Volatile components

Several innovative and novel extraction techniques have been employed to isolate volatile components of fennel in different conditions which have resulted in variation both qualitatively and quantitatively. For example, comparison of the volatile composition of fennel has been carried out using direct thermal desorption (DTD) coupled to gas chromatography-mass spectrometry. DTD allowed a high recovery of volatiles from small sample sizes without thermal decomposition. Although a high variability was found among samples, showing clear phytochemical differences (11).

The influence of different hydrodistillation conditions was evaluated from the standpoint of essential oil yield and chemical composition from seeds of fennel. Three hydrodistillation conditions were considered. The main constituents of the oils were: anethole (72.27%-74.18%), fenchone (11.32%-16.35%) and methyl chavicol (3.78%-5.29%). The method of distillation significantly affected the essential oil yield and quantitative Composition (12). A comparison of essential oils extracted by super critical carbondioxide ($SCCO_2$) and steam distillation showed different compositions in different species and found that $SCCO_2$ extraction resulted higher yield than steam

distillation (13, 14).

Another study conducted on flower, unripe and ripe fruit oils revealed that major components were estragole (53.08%, 56.11%, and 61.08%), fenchone (13.53%, 19.18%, and 23.46%), and alpha-phellandrene (5.77%, 3.30%, and 0.72%), respectively. Minor qualitative and major quantitative variations for some compounds of essential oils were observed with respect to the different parts of fennel (15). A novel and rapid headspace solvent microextraction followed by gas chromatography-mass spectrometry (HSME-GC-MS) for the analysis of the volatile compounds of fennel is described. A comparison of HSME-GC-MS, solid phase microextraction (SPME)-GC-MS and steam distillation (SD)-GC-MS methods showed that the HSME-GC-MS method was simple, inexpensive and effective and can be used for the analysis of volatile compounds (16).

Further, a subcritical extractor equipped with a three-way inlet valve and an on/off outlet valve has been used for performing subcritical water extractions (SWE) in a continuous manner for the isolation of the essential oil of fennel. The target compounds were removed from the aqueous extract by a single extraction with 5 ml hexane, determined by gas-chromatography-flame ionization (GC-FID) and identified by mass spectrometry (MS). The proposed extraction method has been compared with both hydrodistillation and dichloromethane manual extraction. Better results have been obtained with the proposed method in terms of rapidity, efficiency, cleanliness and possibility of manipulating the composition of the extract (17). Microscopic Raman studies have enabled direct analysis of chemical composition in the plant and demonstrated that anethole, which is the main essential oil component, is present in the whole mericarp with highest concentration at the top of the fruit (18, 19).

It should be noted that trans-anethole, estragole, fenchone, alpha phellandrene, methyl chavicol, *p*-allyl anisole are the most abundant compounds so far determined from this plant (20-22). Although most of these compounds are known, their complete pharmacological properties remain, in general, underdetermined.

Non-volatile Components

Recently, a few researchers have determined to prepare various extracts from fennel or fennel waste (marc remained after separation of volatile oil) to isolate non volatile components from the drug. Studies conducted on different varieties of fennel at different conditions demonstrated the presence of some potent phenolic and flavonoidal components are presented here.

Total phenolic contents calculated as gallic acid equivalents in wild fennel was found higher than those of both medicinal and edible fennels (23). A bioguided isolation of an aqueous extract of fennel waste led to the isolation of 12 major phenolic compounds. Eight new compounds were isolated and identified. 3-caffeoylquinic acid, 4-caffeoylquinic acid, 1,5-O-dicaffeoylquinic acid, rosmarinic acid, eriodictyol-7-O-rutinoside, quercetin-3-O-galactoside, kaempferol-3-O-rutinoside, and kaempferol-3-O-glucoside (24). Qualitative and quantitative differences among the constituents in various fennel teas prepared by classical infusion, microwave decoction, and dissolution were reported. Chlorogenic acid, quercetin-3-O-beta-D-glucuronide were identified by HPLC-DAD and HPLC-MS as constituents of fennel teas. In addition, minor unidentified flavonol constituents were found in two teas (25). Two diglucoside stilbene trimers and a benzoisofuranone derivative were isolated from fennel fruit (26). Seven phenolic acids; viz., tannic, gallic, caffeic, cinnamic, chlorogenic, ferulic and vanillic acids were identified on the basis of their retention time with standard compounds and co-chromatography (27). Identification of water-soluble phenolic compounds in fennel waste reported forty-two phenolic substances, 27 of which had not previously been reported in fennel, including hydroxycinnamic acid derivatives, flavonoid glycosides, and flavonoid aglycons (28). A reversed-phase HPLC method for analyzing phenolic compounds in fennel has also been developed. The method was validated for the major phenolic compounds present in fennel plant material: 3-O-caffeoylquinic acid (3-CQA), chlorogenic acid, 4-O-caffeoylquinic acid (4-CQA), eriocitrin, rutin, miquelianin, 1,3-O-dicaffeoylquinic acid (1,3-diCQA),1,5-O-dicaffeoylquinic acid (1,5-diCQA), 1,4-O-dicaffeoylquinic acid (1,4-diCQA) and rosmarinic acid (29).

Therapeutic Potential of *Foeniculum vulgare*

Antibacterial and antifungal activity

Several studies have been conducted to screen the antibacterial and antifungal properties reveals that the volatile oil isolated from fennel fruit may be useful as natural and safe additives for promoting the safety and quality of ready-to-eat vegetables due to their inhibitory properties for some food borne pathogens (30-35). Qualitative and quantitative assays were carried out using cup plate method, microdilution method, vapour contact assay and paper disc diffusion method. While observing the therapeutic activity against most of the pathogenic bacteria, gram-positive bacteria were more sensitive to essential oil than gram-negative bacteria and *Listeria monocytogenes* strains were among the most sensitive while *Pseudomonas* spp. were the most resistant (30). The oils exerted varying levels of antifungal effects on the experimental mycelial growth of fungi depending on the doses and experimental assays used (36, 37), The inhibiting effects of essential oil in vapour phase were generally higher than those in liquid state (370. Marked antifungal activity has been observed against *Sclerotinia sclerotiorum*, *Alternaria alternata*, *Fusarium oxysporum*, *Rhizoctonia solani* and *Phytophthora infestans* (36-38).

Antibacterial activity of fennel plant other than essential oil has also been attempted. A phenyl propanoid derivative, dillapional was found to be a antimicrobial principle of the stems of *Foeniculum vulgare* against *Bacillus subtilis*, *Aspergillus niger* and *Cladosporium cladosporioides*, respectively. A coumarin derivative, scopoletin was also isolated as marginally antimicrobial agent along with inactive compounds, dillapiol, bergapten, imperatorin and psolaren from this plant (39).

Antioxidant activity - Aqueous extract of fennel was investigated in comparison with the known antioxidant ascorbic acid *in vitro* studies. The amount of aqueous extract of

this umbelliferous fruit and ascorbic acid needed for 50% scavenging of superoxide radicals was found to be 205 μg and 260 μg, the amount needed for 50% inhibition of lipid peroxide was 4600 μg and 5000 μg and the quantity needed for 50% inhibition of hydroxyl radicals was 700 μg and 4500 μg respectively (40). Methanolic extract has significantly increased the plasma superoxide dismutase (SOD) and catalase activities and the high density lipoprotein-cholesterol level. On the contrary, the malondialdehyde (MDA) (as a measure of lipid peroxidation) level was significantly decreased (41). A bioguided isolation of an aqueous extract of fennel waste led to the isolation of eight antioxidant compounds which exhibited a strong antiradical scavenging activity (42). The aqueous extract of *Foeniculum vulgare* showed a greatest nitric oxide scavenging effect of 79.75% at 62.5 μg/mL as compared to the positive control (43). Fennel was evaluated for its radical scavenging activity by the DPPH, NBT/hypoxanthine superoxide, and OH/luminol chemiluminescence methods, and their antioxidant activity by the beta-carotene blenching test. As a result, the distilled plant material was found to exhibit better antioxidant and radical scavenging activities than the nondistilled material (44). Ethanolic extract of fennel has also exhibited good radical scavenging activity (45). A significant enhancement in the activities of antioxidant enzymes were observed especially at 4% and 6% test diets of Fennel. Glyoxalase I activity and the content of reduced glutathione were significantly elevated (46).

Essential oil of fennel has also been observed to have strong radical scavenging and has a strong protective effect against lipid peroxidation when compared with standard compound like trolox, vitamin E and tert-butyl hydroxyl anisole (BHA) (47-51).

Insecticidal/mosquito repellent activity

Two laboratory-reared mosquito species, *Anopheles dirus*, the major malaria vector in Thailand, and *Aedes aegypti*, the main vector of dengue and dengue hemorrhagic fever in urban areas, were used to investigate larvicidal potential against mosquito vectors. The volatile oil of fennel exerted significant larvicidal activity against the two mosquito species after 24-h exposure (52). The insecticidal activities of essential oil extracts from leaves, flowers and roots of fennel against fourth-instar larvae of the mosquito *Culex*, *pipiens*, *molestus* and *forskal*, were determined. Extracts of *Foeniculum vulgare* Mill were found to be toxic with LC50 values of 24.5 mg/litre (53). In paddy field tests with five human volunteers, 5% and 8% fennel oil-containing aerosol and cream produced 84% and 70% repellency, respectively, at 90 min after exposure against female

Aedes aegypti (54). In a skin test with female mosquitoes, at a dose of 0.4 mg/cm, the biologically active isolated constituents of fennel, (+)-fenchone and (Z)-9-octadecenoic acid exhibited moderate repellent activity at 30 min after treatment (55).

Above studies observed with mixed responses varied with insect species, compound, dose and exposure time indicating that the insecticidal activity of test compounds was largely attributable to fumigant action and merit further study as potential mosquito repellent agents or as lead compounds.

Analgesic and antispasmodic activity

Oral administration (200 mg/kg) of *Foeniculum vulgare* fruit methanolic extract exhibited inhibitory effects against acute and subacute inflammatory diseases and type IV allergic reactions and showed a central analgesic effect (42). Fennel extract and fennel seed oil emulsion has decreased the intensity of infantile colic and found to be superior to placebo (56-59). Compared with mefenemic acid, the essence of fennel can be used as a safe and effective herbal drug for primary dysmenorrhea, however, it may have a lower potency than mefenamic acid in the dosages used for this study (60-62).

Anticancer activity

TNF-mediated signaling, which is associated with both inflammation and carcinogenesis has been screened and observed that anethole is a potent inhibitor of TNF-induced NF-kappa B activation (an early response) as monitored by electrophoretic mobility shift assay, IkappaBalpha phosphorylation and degradation, and NF-kappaB reporter gene expression. Results demonstrate that anethole inhibits TNF-induced cellular responses, which may explain its role in suppression of inflammation and carcinogenesis (63). Fennel has inhibited the growth of prostate tumor xenografts, possibly in part by antiangiogenic mechanisms (64). Some other studies have also claimed the anticancer properties of fennel and suggest further investigations (65-68).

Other pharmacological actions reported

In addition, fennel essential oil and fennel extracts have also been screened for possible therapeutic potential against several other health disorders and reported to exert beneficial effect in gastric disturbances (69, 70), respiratory disorders (71-740), glaucoma (95-78), hypertension (79), diabetes (80), CNS disorders (81, 82), obesity (83), skin infections (84-86), tuberculosis (87) and also can be used as anticoagulant (88-90), hepatoprotective (91, 92) and diuretic (93).

Summary, concluding remarks and perspectives

An herb of ancient medical repute, believed to convey longevity, courage and strength in folklore medicines. It was also used to ward off evil spirits, strengthen the eyesight and to neutralize poisons. In eastern and western herbalist it is considered good for obstructions of the liver, spleen and gall bladder and for digestive complaints such as colic, indigestion, nausea and flatulence (an ingredient of children's 'gripe water').

This review discussed the current knowledge of chemistry, pharmacological potential and compounds isolated from volatile oil as well as extracts of this plant. Prominent pharmacological reports are available regarding the therapeutic potential of this plant as antibacterial, antifungal, antioxidant and mosquito repellent. However, well controlled double-binding clinical trials are lacking. Phytochemical studies carried out on this plant reveal great class of compounds including volatile components, phenols and flavonoids seems to be responsible for observed therapeutic actions.

Altogether, this data strongly support the view that this plant has potential beneficial therapeutic actions against certain

body disorders. However, some important questions need adequate answers. For example, a re-evaluation through well controlled double-binding study using a large number of patients, is still necessary for proper assessment of their, efficacious and possible side effects, a better analysis of the mechanism of actions, and an evaluation of the synergistic action among the active principles present in this plant needs to be carried out before their use in clinical practice is adopted. Finally, the clinical use of this plant as phytomedicine will depend on the establishment of sensitive analytical methodologies necessary for standardization of the numerous secondary metabolites existing in such herbal preparations.

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