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Fennel (*Foeniculum vulgare* Mill.): A Common Spice with Unique Medicinal Properties

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Abstract

Introduction: *Foeniculum vulgare* is a perennial, aromatic plant belonging to Apiaceae (Umbelliferae) family. The fruits, commonly referred to as seeds, are ridged, aromatic and oblong or ellipsoid shaped. Originally indigenous to the Mediterranean region, it has now been naturalized and cultivated throughout the world and is universally known as fennel and by more than 100 other names. The dried fruits and aerial parts have widely been used since ancient times in culinary and traditional folk medicines in many cultures around the world. It was well-known to the ancient Egyptians, Greeks, Romans and Chinese. Hippocrates and Dioscorides described it as a diuretic and Emmenagogue and to strengthen eyesight. The fruits are reputed as carminative, stomachic, diuretic, Emmenagogue and Galactagogue and to promote menstruation and facilitate birth.

Photochemical and Pharmacological Studies: Fennel fruits contain carbohydrates, alkaloids, Phytosterols, phenols, tannins and flavonoids. They are also a rich source of dietary fiber, protein, calcium, iron, magnesium and manganese. Pharmacologically, the fruits possess antioxidant, anti-inflammatory, antispasmodic, diuretic, antihypertensive, antimicrobial, Gastro protective, estrogenic, Hepatoprotective and antithrombotic activities.

Discussion and Conclusion: This article reviews the use of fennel in medical practices in various parts of the world and reflects upon the scientific studies conducted and how they reconcile with its traditional uses. The clinical studies in small number of patients revealed several clinical effects but are not sufficiently wide ranging and have not been reproduced in numbers that would make them conclusive. Randomized, double-blinded, placebo-controlled clinical trials would establish the clinical usefulness of fennel in a scientific manner.

Keywords: Fennel; F*oeniculum Vulgare*; Anethole; Fenchone; Estragole

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Introduction

Historical perspective and medicinal uses

*Foeniculum Vulgare*is usually a perennial, aromatic plant belonging to Apiaceae (Umbelliferae) family with many subspecies and varieties. *F. vulgare* subsp. *vulgare var.* Dulce is called sweet fennel, while *F. vulgare* mill. Subsp. *vulgare var. vulgare* is referred to as bitter fennel. Mostly these two varieties are commercially available and are used medicinally. The plant grows wildly in Mediterranean region and in European countries of temperate climate but is now cultivated in most parts of the world for commercial purposes. The fruits commonly referred to as seeds are ridged, oblong or ellipsoid shaped, aromatic and are universally known as fennel and by more than 100 other names throughout the world and have been used medicinally since ancient times as one of the ancient Saxon people's nine sacred herbs, fennel was credited with the power to cure and was valued as a magic herb [1,2]. In the middle ages, it was draped over doorways on midsummer's eve to protect the household from evil spirits [3]. Fennel is also one of the most frequently quoted plants in the chilandar medical codex, the best preserved medieval Serbian manuscript on European medical science from the 12th to 15th centuries [4]. Famous Greek physicians, Hippocrates and Dioscorides mentioned fennel as a diuretic and Emmenagogue and its juice was supposed to sharpen the eyesight [5]. The fruits are especially reputed to increase milk secretion, promote menstruation, facilitate birth, alleviate the symptoms of the male climacteric and increase libido [6]. In Indian traditional medicines, it is considered a stimulant, carminative, aromatic, stomachic, Emmenagogue and Galactagogue; the fennel fruit water is traditionally used to relieve flatulent colic and also as a diuretic and diaphoretic in children and infants. A hot infusion is used to treat amenorrhea and to improve lactation, [5,7-12] to improve eyesight and to open liver and spleen obstructions [7]. In

Europe and Mediterranean countries, fennel is traditionally used as antispasmodic, diuretic, anti-inflammatory, analgesic, secret motor, Galactagogue, eye lotion and antioxidant remedy; topically, fennel powder is used as a poultice for snake bites and fennel infusions are used in Europe for nursing babies to prevent flatulence and colic spasm [3]. It is approved in Europe for use in gi disorders in children above the age of 4 years since November. 2005 by the committee on herbal medicinal products (hmpc) of the European medicines agency, but is not recommended for use for more than two weeks [13]. It is one of the most commonly consumed herbs by more than a quarter of Italian pregnant women every day for at least 3 months during pregnancy [14]. A subspecies of fennel, *F. vulgare* subsp. *piperitum*, is used for mouth ulcers in the Basilicata region of southern Italy in Portugal, it is highly recommended for treatment of diabetes, bronchitis and chronic coughs, and for kidney stones [15,16]. In Mexican traditional medicine, a decoction is used as a galactagogue and to treat tuberculosis and other respiratory diseases [17,18]. In Palestine, wildly grown fennel is traditionally used as a regular part of diet and as a popular digestive stimulant in north-east Lebanon [19,20]. In Chinese medicine, it is regarded carminative, stomachic and stimulant, and is used to relieve chills, abdominal distension, vomiting and diarrhea [21,22]. Fennel leaves infusion is also used to treat infant's stomach-ache and the seeds are used by adults to dispel gases in Guyana and Surinam and boiled or roasted roots are used for the treatment of gonorrhea in east Africa [23,24]. Fennel essential oil is also widely used as a flavoring agent in products such as liqueurs, bread, cheese and as an ingredient of cosmetics and pharmaceutical products [3,25-29].

Photo constituents

Fennel fruits contain alkaloids, carbohydrates, Phytosterols, phenols, tannins, coumarins and flavonoids as nonvolatile substances; the acetone extract is richer in phenols, while methanol extract contains higher amounts of flavonoids [30]. Kaur et al. [31] reported the presence of alkaloids, flavonoids, tannins, saponins and trace amounts of cardiac glycosides in hot water fruit extract and methanol extract of fruit sample from Egypt was reported to contain flavonoids, terpenoids, alkaloids, phenols and sterols; which had estragole (methyl chavicol) (71.1%) as the predominant alcohol, gallic acid (18.9%) as the major phenolic compound and l-limonene (11.9%) as the most prevalent monoterpene hydrocarbon [32]. Major phenolic compounds identified in fennel include 3-o-caffeoylquinic acid, chlorogenic acid, 4-o-caffeoylquinic acid, eriocitrin, rutin, miquelianin, 1,3-o-dicaffeoylquinic acid, 1,5-o-dicaffeoylquinic acid, 1,4-o-dicaffeoylquinic acid and rosmarinic acid; [33] identified flavone (OL)-o-glycosides are quercetin 3-glucuronide, isoquercitrin, rutin, and quercetin 3-arabinoside; other phenols reported are kaempferol 3-glucuronide and kaempferol 3-arabinoside [34]. Bergapten, columbianetin, osthenol, psoralen, scoparone, seselin, vanillin, beta-sistosterol and stigmasterol have also been identified in fruits [35]. Two diglucoside stilbene trimers and a benzoisofuranone derivative have also been isolated from the fruits [36]. The elements present in fennel fruits from Ethiopia were reported as calcium, magnesium, iron, manganese, copper, chromium, cobalt, zinc, nickel and cadmium [2]. Fennel is reported as one of the plant sources with highest amounts of calcium, potassium, sodium and phosphorus [1].

The method of distillation significantly affects the yield and qualitative composition of the essential oil [37]. Essential oil composition also varies depending on the maturation stages of the plant [38]. The yield of Turkish essential oil (5.0 ml/kg) and content of trans-anethole are very low (34.8%), whereas yield of essential oil is maximum in fennel from Norway and Austria (50.7 ml/kg and 50.5 ml/kg), respectively; these samples are richer in Fenchone (21.2% and 22.8%, respectively), but contain less trans-anethole (64.6% to 63.7%) than samples from Estonia and Moldova (82.0% and 80.9%) [39]. In fennel samples collected from the wild population in the center and south of Portugal, the yields of essential oils varied greatly from 1.1% to 2.9%, and the main constituents, trans-anethole (7.9% to 77.7%), Fenchone (16.9% to 34.7%) and estragole (2.5% to 66.0%) also showed great variations [40]. In general, fennel oil extracted by either distillation-extraction or supercritical fluid extraction shows similar compositions, with trans-anethole, estragole and Fenchone as the main components [37,41-42]. Trans-anethole (85.63%) is generally the predominant constituent of the oil [43-47], while estragole is found in small amounts (2.87%), and the quantity of Fenchone is <1% [45]. Trans-anethole (69.8%) and limonene (22.5%), though, were identified as the major constituents of essential oil in fennel samples cultivated in southeastern Brazil [48] and Miguel et al. [49] reported estragole as the dominant constituent in the fruit essential oil of samples from Portugal, and trans-anethole, alpha-pinene and limonene being the main components of dried aerial parts essential oil. In samples of essential oil of fennel grown under different climatic conditions in Romania, major compounds identified in all samples were trans-anethole, estragole, fenchone, limonene, alpha-pinene and gamma-terpinene [50] and fennel oil samples from Egypt also showed trans-anethole, estragole, fenchone and limonene as the major constituents [51]. Essential oils obtained from various wild Italian varieties contained five chemical groups characterized by (i) alpha-phell andrene, methyl chavicol (estragole) and trans-anethole; (ii) alpha-pinene, limonene and trans-anethole; (iii) methyl chavicol and alpha-phell andrene; (iv) methyl chavicol and alpha-pinene; and (v) alpha-phell andrene [52].

In Chinese medicine various frying methods are used before the fruits are incorporated in poly herbal preparations. After different frying methods, contents of all twenty-four ingredients of the volatile oil from these fruits were changed, and eighteen new compounds, including Linalyl acetate, farnesene, p-allyiphenyl aromatic oxide, and Menthone and hexyl octanoate were created; however, trans-anethole remained the largest of the effective ingredients in the fried samples [53].

Estragole, an isomer of anethole, is regarded carcinogenic and genotoxic by the hmpc of European medicine agency. Estragole is rapidly metabolized in humans and excreted in urine as 1'-hydroxyestragole [54] and the hmpc recommends that the total human daily intake of estragole from all food sources should not exceed 0.07 mg/kg [3]. Nevertheless, contents of estragole in commercial teabags and loose fruits vary widely. For example, estragole contents in teas made from teabags ranged from 241 to 2,058 μg/l, while in diluted instant teas they were from 9 to 912 μg/l, estragole contents ranged from 251 to 1718 μg/l in unpackaged fruits (seeds) [55] a study among finish consumers, though, found daily consumption of estragole due to fennel containing plant food supplements to be moderate and not detrimental to health [56].

Results

Experimental studies

Antioxidant effects: Aqueous fruit extract (AE) demonstrates

direct and highly significant *in vitro* nitric oxide scavenging [57] and antioxidant activities [58-59] and improves activities of antioxidant enzymes in trichloroacetic acid-exposed rats [60]. The quantity of AE required for 50% inhibition of hydroxyl radicals was 700 microg compared to 4500 microg for ascorbic acid; whereas, scavenging of superoxide radicals by 50% required 205 microg fennels *vs.* 260 microg ascorbic acid [59]. Although aqueous, methanol acetone and other extracts of fruits have all been reported to possess antioxidant activity, the methanol and acetone extracts are comparable to activity of butyrate hydroxyl toluene because acetone fruit extract is reported to have comparatively high amount of total phenolics, whereas methanol extract had highest amount of total flavonoids [30,32,61]. Moderate antioxidant activity of ethanol fruit extract was, however, independent of the total flavonoid content present in the extract [62]. Four coumarins, isolated from the methanol extract, have shown excellent *in vitro* antioxidant and anti-inflammatory activities [63]. Both methanol extract and essential oil also significantly improved activities of antioxidant enzymes and inhibited lipid peroxidation [64-66]. The essential oil with predominant trans-anethole content showed a significantly higher antioxidant activity with low IC50 value [67] and demonstrated *in vitro* antioxidant capacities comparable to that of alpha-tocopherol and butyrate hydroxyl toluene [68]. Essential oil is, however, rapidly auto-oxidized by light, and the rate of its oxidation is reported to be slower in the dark [69]. The shoots have the highest radical-scavenging activity and lipid peroxidation inhibition capacity, due to highest content of phenolics and ascorbic acid, and high concentration of tocopherol and allegedly are the only part to contain flavonoids, but Goswami et al. [30] reported the presence of flavonoids in fruits too [30]. In early fruiting stage, aerial parts contain lowest flavonoid contents and higher phenolic acid content and aerial parts infusion rather than decoction shows better *in vitro* antioxidant activity [70,71]. The length of storage period of aerial parts, however, significantly affects the antioxidant content and antioxidant activity [72].

Antimicrobial effects: Significant *in vitro* antibacterial activity of hot aqueous and acetone fruit extracts against *Enterococcus faecalis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi, Salmonella typhimurium and Shigella flexneri* has been reported. The ambient temperature water extract showed weaker antibacterial activity, whereas the activity was completely lost in the boiling water extract and the acetone extract was active with significantly lower Minimum Inhibitory Concentration (MIC) values than the water extract [31]. While a number of reports indicated that the essential oil exhibits insignificant or moderate antibacterial activity against standard strains of *E. coli, S. aureus, P. aeruginosa, Bacillus subtilis, Bacillus megaterium, and Bacillus cereus* [51,73-75]; significant *in vitro* activity of essential oil against various strains of *S. aureus and E. coli* [40,50,76], against *Salmonella enterica, Listeria monocytogenes, B. cereus, Candidaalbicans, Aspergillus niger, and Penicillium spp* and synergistic activity with amoxicillin or tetracycline against *E. coli, Sarcina lutea and B. subtilis* strains have been reported [40,50,76]. The essential oil also exhibited *in vitro* antifungal activity against *C. albicans*, [50-51,77] aspergillus species [51,78] and potent activity against dermatophytes *Trichophyton rubrum, T. tonsurans, T. mentagrophytes and Micro sporum gypseum*, better than the standard antifungal agents, fluconazole and amphotericin b[79]. Jazani et al. [80] reported the essential oil bactericidal against isolates of multi-drug resistant *Acinetobacter baumannii*, a gram negative coccobacillus, increasingly responsible for nosocomial infections. Essential oil of Turkish fennel was also reported effective against *E. coli, L. monocytogenes, S. typhimurium, and S. aureus*, [43] *E. faecalis, Staphylococcusepidermidis and S. aureus*; against *Morganella morganii, Proteus mirabilis, Salmonella enteritidis, and P. aeruginosa* [40], Strains of klebsiella Pneumonia producing Extended-Spectrum Beta-Lactamase (ESBL) enzyme [81]. Moderate activity of methanol extract against 15 strains of *Helicobacter pylori* with an MIC of 50 mcg/ml [82], significant activity of hydro-ethanol extract against *campylobacter jejuni* [83] and against the multidrug resistant *Mycobacterium tuberculosis* has also been reported [18]. Fennel oil, used at sub-inhibitory concentrations, also decreased the expression of *S. aureus* exotoxins, including α-toxin, *Staphylococcal* enterotoxins and toxic shock syndrome toxin 1 [47].

Gastro protective effect: Pretreatment with fennel water extract significantly reduced ethanol-induced gastric damage in rats, which was suggested to be due to reduction in lipid peroxidation and augmentation in the antioxidant activity [84]. The water extract is reported to increase gastric acid secretion by more than three times of basal secretion in rats that was not blocked by atropine; but significantly reduced basal acid secretion in aspirin-induced gastric mucosal damage [85]. Oral administration of essential oil and anethole is also significantly protective against ethanol-induced gastric lesions in rats [86]. The antioxidant activity of phenol contents is partly credited for the anti-ulcer effects [84].

Anti-inflammatory effect: Methanol fruit extract exhibited inhibitory effects against both acute and sub-acute inflammation and a central analgesic effect, and significantly increased plasma antioxidant enzymes activities and the HDL-cholesterol level [64]. Four coumarins isolated from the fruits showed excellent *in vitro* antioxidant activity and imperator in had the greatest anti-inflammatory and antioxidant activities, inhibiting pro-inflammatory cytokines production, including interleukin-6 and tumor necrosis factor-α (TNF-α) in Lipopolysaccharides (LPS)-stimulated raw 264.7 cells [62]. Essential oils from the aerial parts and fruits are also reported to inhibit 5-lipoxygenase enzyme [49].

Estrogenic effects: A number of experimental studies point to the estrogenic effects of fennel. Water extract shows renoprotective effects in experimental polycystic ovary syndrome in rats [87] and prevents ovariectomy-induced bone loss, reducing both osteoclast differentiation and function [88]. Administration of acetone fruit extract also exhibited oestrogenic activity [89] increasing weight of mammary glands [89] oviducts of ovariectomized rats [90] vaginal cornification and oestrus cycle in female rats, and significantly reducing protein contents of testes and vas deferens in male rats [89].

Cardiovascular effects: It is one of the commonly used plants to lower blood pressure that acts by causing diuresis, increasing excretion of sodium and water from the body [91]. Oral fruit water extract lowered systolic blood pressure of spontaneously hypertensive rats and increased water, sodium and potassium excretion [92]. Intravenous administration of boiled water extract of leaves also significantly lowered arterial blood pressure, whereas the non-boiled water extract showed insignificant hypotensive activity [93]. An increase in both RBC and WBC counts of rats was observed after alternate day oral administration of the hydro alcohol extract for 30 days [94]. Oral administration of essential oil and anethole to mice produced a significant antithrombotic activity and both inhibited platelet aggregation, and prevented thrombin-induced clot retraction [86,95]. Co-administration of fennel essential oil with Emamectin

Table: Selected Pharmacological and Clinical Observations of Fennel (*Foeniculum vulgare*).

S. No.	Study Type	Study Year	Part Used	Extract Type/Essential oil	Study Subjects	Reference No.
Experimental						
1	Antioxidant	2004, 2008, 2009, 2011, 2014	Fruits	Water, Methanol, Acetone, and Ethanol Extracts	*In Vitro*	[30,32,58,59,61,69]
2	Antioxidant	2008	Fruits	Water Infusion	Rats	[60]
3	Antioxidant	2000, 2011	Fruits	Essential oil	*In Vitro*	[66,67]
4	Antioxidant	2009	Aerial Parts		*In Vitro*	[70]
5	Antioxidant	2009	Fruits	Coumarins	*In Vitro*	[63]
6	Antioxidant	2015	Fruits	Ethanol Extract	*In Vitro*	[62]
7	Nitric Oxide Scavenging	2003	Fruits	Water Extract	*In Vitro*	[57]
8	Antimicrobial	2009	Fruits	Hot Water and Acetone Extracts	*E. faecalis*, *S. aureus*, *E. coli*, *P. aeruginosa*, *S. typhi*, *S. typhimurium, S. flexneri*	[31]
9	Antimicrobial	2015, 2004, 2008, 2011, 2002, 2002, 2007, 2010, 2010, 2015, 2009, 2011	Fruits	Essential oil	*E. coli*, *S. aureus*, *P. aeruginosa*, *B. subtilis, B. megaterium, B. cereus, S. enterica*, *L. monocytogenes*, *C. albicans*, *A. niger*, *T. rub rum*, *T. tonsurans*, *T. mentagrophytes M. gypseum, A. baumannii, S. typhimurium*, *E. faecalis*, *S. epidermidis Morganella morganii, P. mirabilis*, *S. enteritidis*, strains of *K. pneumonia*	[40,43,50,51,73-76,78-81]
10	Antimicrobial	2005	Fruits	Methanol Extract	15 strains of *H.pylori*	[82]
11	Antimicrobial	2008, 2010	Fruits	Hydro-ethanol extract	*C. jejuni*, MDR *M. tuberculosis*	[18,83]
12	Antispasmodic	2003	Fruits	Oil emulsion	Infants	[108]
13	Gastric Antiulcer	2000, 2007	Fruits	Water Extract	Rats	[84,85]
14	Gastric Antiulcer	2007	Fruits	Essential oil	Rats	[86]
15	Anti inflammatory	2004	Fruits	Methanol Extract		[64]
16	Antihypertensive	2001	Fruits	Water Extract	SHR	[92]
17	Antihypertensive	1998	Leaves	Water Extract (I.V.)	Rats	[93]
18	Antithrombotic	2007, 2006	Fruits	Essential oil	Mice, Rats	[86,95]
Clinical						
19	Analgesic	2013, 2006, 2003, 2012	Fruits	Extract or Essence	Young Women with Primary Dysmenorrhea	[108-111]
20	Antispasmodic	2003	Fruits	Fennel Oil Emulsion	Infants (2 to 12 weeks old)	[106]
21	Anorexogenic	2015	Fruits	Tea	Overweight Women	[107]
22	Vaginal Symptoms	2016	Fruits	Vaginal Cream	Postmenopausal Women	[112]
23	Idiopathic Hirsutism	2003, 2014	Fruits	Cream and Gel	Women	[113,114]

Abbreviations: *A. baumannii*: *Acinetobacter baumannii*; *A. niger*: *Aspergillus niger*; *B. cereus*: *Bacillus cereus*; *B. megaterium*: *Bacillus megaterium*; *epidermidis*; *B.* subtilis: *Bacillus subtilis*; *C. jejuni*: *Campylobacter jejuni*; *C. albicans*: *Candida albicans*; *E. coli*: *Escherichia coli*; *E. faecalis*: *Enterococcus faecalis*; *H. pylori*: *Helicobacter pylori*; *K. pneumonia*: *Klebsiella pneumonia*; *L. monocytogenes*: *Listeria monocytogenes*; *M. gypseum*: *Microsporum gypseum*; *M. morganii*: *Morganella morganii*; *M. tuberculosis*: *Mycobacterium tuberculosis*; *P. aeruginosa*: *Pseudomonas aeruginosa*; *P. mirabilis: Proteus mirabilis*; *S. aureus*: *Staphylococcus aureus*; *S. epidermidis*: *Staphylococcusepidermidis*; *S. typhimurium*: *Salmonella typhimurium*; *S. enterica*: *Salmonella enterica*; *S. enteritidis*: *Salmonella enteritidis*; *S. typhi: Salmonella typhi*; *S. flexneri: Shigella flexneri*; *T. mentagrophytes*: *Trichophyton mentagrophytes*; *T. tonsurans*: *Trichophyton tonsurans*; *T. r Trichophyton mentagrophytes ubrum: Trichophyton rub rum*

Benzoate (EB), an avermectin insecticide used extensively in pest control on vegetable and field crops, to rats ameliorated EB-induced coagulative necrosis and blood vessels congestion of the liver and necrosis of the white pulp of the spleen [96]. Topical application of water fruit extract also significantly reduced intraocular pressure in both normotensive and experimental glaucoma model in rabbits [97].

Miscellaneous effects: While Joshi et al. [98] reported that administration of methanol extract of the whole plant for eight successive days ameliorated scopolamine-induced amnesic effect, aging-induced memory deficits, and significantly inhibited Acetylcholinesterase (AChE) in Mice et al. [99] reported significant ache and Butyrylcholinesterase inhibitory activity of the essential oil, more than any single active component, Mata et al. [100] and Aazza et al. [66] reported poor to moderate *in vitro* ache inhibitory activity of fennel oil. The essential oil of aerial parts also exhibited potential anxiolytic activity in mice [101]. Ethanol extract, and essential oil also significantly produce *in vitro* relaxant effect on methacholine-induced contraction of tracheal chains; calcium channels inhibition was not a contributing mechanism of the relaxant effect [102]. Fennel supplementation in diet protected rats against cyclosporine-nephrotoxicity [103] and the essential oil potently protected against ccl4-hepatotoxicity in rats [104]. The fruit extract was also reported to exhibit *in vitro* immuno-modulatory Nf kappaB activities [105].

Clinical studies: Results of relevant clinical studies on fennel have been presented in table 1. A number of clinical studies have shown significant antispasmodic, analgesic, and putative estrogenic activities of fennel. In a Randomized, Placebo-Controlled Trial (RCT), use of fennel oil emulsion relieved colic in 65% of 2 to 12 weeks

old infants, compared to 23.7% infants treated with placebo [106]. Drinking fennel tea followed by buffet lunch in overweight Korean women significantly decreased appetite and food consumption, and increased feeling of fullness in a placebo-controlled, single-blinded, randomized, crossover study [107]. Several clinical studies in young high-school Iranian girls with moderate to severe dysmenorrheal showed that treatment with fennel extract or essence of fennel's fruit effectively relieved menstrual pain, comparable to mefenamic acid [108-111]. However, patients complained of the odor and unpleasant fennel taste and 16% patients withdrew from one study for this reason [110]. In a double-blind RCT, once daily intravaginal application of fennel 5% vaginal cream in postmenopausal women for 8 weeks, significantly improved postmenopausal vaginal symptoms, increasing number of superficial cells and significantly decreasing the vaginal ph [112]. In another double-blind RCT in women with mild to moderate idiopathic hirsutism, topical application of 3% fennel gel [113] or application of cream containing 2% ethanol fruit extract significantly reduced hair thickness after 24 weeks of treatment compared to placebo [114]. Topical application of 5% and 8% fennel oil-containing aerosol and cream produced 84% and 70% repellency against mosquitoes after 90 min of exposure, respectively [115]. An interesting observation reported was that inhalation of fennel essential oil caused a 1.5 to 2.5 fold increase in relative sympathetic activity in normal healthy subjects [116] human adverse effects and toxicity: the fruits used under guidance of an herbalist and even without supervision but in moderate use, are generally very safe. The European medicines agency lists allergic reactions affecting skin or the respiratory system as the most common side effect. Intoxication in infants resulting in methemoglobinemia after eating homemade fennel purée has been reported, though all patients recovered after treatment with methylene blue [117]. Long-term use to relieve gas and to regulate intestinal function in children is also suggested to cause premature thelarche [118]. An epileptic patient, with well-controlled epilepsy, developed typical generalized tonic-clonic seizures after consuming a number of cakes containing an unknown quantity of fennel essential oil. Therefore, caution must be exercised while using fennel essential oil in patients with epilepsy [119].

Animal toxicity: Ethanol extract is reported nonlethal and nontoxic to mice up to a single oral dose of 3 g/kg [120-121] and chronic administration of the extract in a dose of 100 mg/kg/day for 90 days caused only significant weight gain in male mice [120]. The oral LD50 of the essential oil in rats is reported to be 1.32 g/kg [122].

CYP450 and potential for drug-drug interactions: water fennel extract is reported to potently inhibit CYP2D6 and CYP3A4 potentially causing a clinically relevant inhibition of intestinal CYP3A4 that may influence the pharmacokinetics of drugs metabolized by this isozyme [123,124]. War far in is a drug with a narrow therapeutic window, and one of its main metabolites, 10-hydroxywarfarin is formed by metabolism mediated by CYP3A4, use of fennel with war far in may thus result in an increased effect of war far in, and increased chances of bleeding [125]. Concomitant administration of water extract with ciprofloxacin to rats was also reported to affect absorption, distribution and elimination, significantly lowering maximum plasma concentration (Cmax), area under the curve (AUC) and urinary recovery of ciprofloxacin [126] methanol fruit extract also time-dependently inhibited CYP3A4 in human liver microsomes [127] 5-methoxypsoralen (5-MOP) has been suggested as responsible for the CYP3A4 inhibitory activity [128].

Discussion

From the foregoing description, it is apparent that there are very limited randomized, double-blind, placebo-controlled clinical studies on fennel, except its anti-flatulent and anti-colic effects, to draw any conclusions about various medicinal uses in an objective scientific manner. Nevertheless, its use since ancient times is a testament for its usefulness in certain conditions. It is now established that a number of diseases have cellular damage due to oxidative stress as a component of their pathology. Fennel contains significant amounts of antioxidant substances, such as phenolic compounds and flavonoids that display a broad spectrum of physiological activities and protect against various disease processes. Various extracts of fennel, its essential oil and coumarins isolated from the methanol extract have all shown significant *in vitro* free radicals scavenging capacity, which might be a factor for its usefulness in certain diseases. Qualitative and quantitative differences in chemical constituents of plant-derived drugs are however responsible for the inconsistencies and variations in the often observed pharmacological or clinical effects. Despite the fact that physicians and botanists from the earlier centuries laid down the rules for collecting (harvesting) the plants for medicinal use from a particular location, in a specific season, month or even time of the day, this aspect was ignored and even ridiculed by the scientific community for a long time and was only relatively lately recognized when quantitative evaluation techniques of chemical constituents became available. Variation in chemical constituents of fennel from different parts of the world is but one such example. The pharmacologically active estrogenic agents are polymers of anethole, such as dianethole and photo anethole. Six several components in fennel fruits, working together, are responsible for the observed effects, as the actions of individual components do not wholly explain these effects [8]. Nevertheless, the clinical studies reported are very few, largely not well organized, and in small number of patients. Therefore, full potentials of fennel could be ascertained only after more blinded RCTS in larger number of patients that could supplement the results obtained in experimental studies.

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