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Review Article

Pharmaceutical, Cosmetic, Perfumery and Food Products of Fennel (*Foenirulum Vulgare*)

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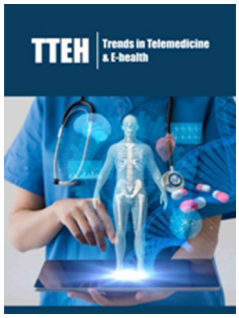

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Abstract

Fennel (*Foenirulum vulgare*) is recommended traditionally for gastrointestinal and neurological disorder, kidney stones, vomiting and diarrhoea, it has also antispasmodic, antiseptic, carminative and antiulcer properties Fennel is rich in vegetable and volatile oils. Plant seeds can be processed into high quality vegetable or essential oils, the remaining portion may find various profitable applications due to their phytochemicals content and antioxidant activity. Besides its nutritional benefits, fennel oil has several positive effects on the skin according to its richness in Mono Unsaturated Fatty Acids (MUFAs) and especially petroselinic acid which can resolve some skin problems, such as dryness. Actually, oilseeds are easily biodegradable and skin lipid compatible and thus, their using in cream formulas could reduce the use of synthetic oil such as paraffin oil. Fennel seed oil is no less important than coriander seed oil in terms of yield and composition as oil yield did not exceed 25.1% with 78.2% of petroselinic acid. Sensory analysis confirmed the positive impact of fennel oils on the cream sensory characteristics oral administration of essential oil and anethole is also significantly protective against ethanol-induced gastric lesions. Water extract shows reno protective effects in polycystic ovary syndrome and prevents ovariectomy-induced bone loss, reducing both osteoclast differentiation and function. 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. The essential oil of aerial parts also exhibited potential anxiolytic activity. Ethanol extract, and essential oil also significantly produce relaxant effect on methacholine-induced contraction of tracheal chains; calcium channels inhibition was not a contributing mechanism of the relaxant effect. Fennel supplementation in diet protected against cyclosporine-nephrotoxicity and the essential oil potently protected against ccl4-hepatotoxicity. Drinking fennel tea followed by buffet lunch in overweight women significantly decreased appetite and food consumption, and increased feeling of fullness. Treatment with fennel extract or essence of fennel's fruit effectively relieved menstrual pain, comparable to mefenamic acid. Topical application of 5% and 8% fennel oil-containing aerosol and cream produced 84% and 70% repellence against mosquitoes after 90min of exposure, respectively.

Keywords: Pharmaceutical; Fennel; Carbohydrates; Nutritional; Polyunsaturated fatty acids

Introduction

Fennel is one of them, generally known as Saunf (*Foeniculum Vulgare*) belonging to Apiece family. Fennel originates from Mediterranean region [1], but it can be found around the world today. It is used as a condiment and culinary spice [2]. Fennel is also a magical remedy for problems related to digestive, endocrine, reproductive and respiratory systems [2]. From the ancient times, it has been in use for constipation, flatulence, diarrhoea and cough [1]. Fennel contains volatile compounds, flavonoids, phenolic compounds, fatty acids, and amino acids [3]. It shows several pharmacological properties like anti-microbial, anti-pyretic, anti-spasmodic, anti-thrombotic, apoptotic, anti-viral, anti-inflammatory, anti-mutagenic, anti-nociceptive, cardiovascular, chemo modulatory, anti-tumour, hepatoprotective, hypoglycemic, hypolipidemic and memory enhancing property [3]. Fennel is being used

in several ayurvedic formulations. It also acts as a galactagogue stimulating milk production in lactating mothers [4]. 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 [3,5]. In the Middle Ages, it was draped over doorways on midsummer's eve to protect the household from evil spirits [6]. 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 [7]. 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 [8]. A subspecies of fennel, *F. vulgare* subsp. piper tum, 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 [9,10]. In Mexican traditional medicine, a decoction is used as a galactagogue and to treat tuberculosis and other respiratory diseases [11]. In Palestine, wildly grown fennel is traditionally used as a regular part of diet and as a popular digestive stimulant in North-East Lebanon [12,13]. 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 [14].

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 [15,16] 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 [17]. 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; [18] 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. Two diglucoside stilbene trimers and a benzoisofuranone derivative have also been isolated from the fruits [19].

Ferme! (*Foenirulum vulgare* Mill.) is a commercially important Apiaceae species from the Mediterranean area and central of Europe and is among the most widespread medicinal plant worldwide, being extensively grown in arid and semi-arid regions as one of the oldest spice plants. It is recommended traditionally for gastrointestinal and neurological disorder, kidney stones, vomiting and diarrhoea, it has also antispasmodic, antiseptic, carminative and antiulcer properties [20]. Recently much attention has been focused on ferme due to the nutritional and health protective value of their seeds that are rich in vegetable and volatile oils [21]. Ferme! seeds are considered also as source of many health beneficial compounds including minerals, vitamins, and others which explain their applications for pharmaceutical, cosmetic, perfumery and food industries [22]. This fatty acid is a positional isomer of oleic acid used as valuable raw material to the synthesis of a series of bio-based compounds that could be of particular interest to chemical industries [23]. Plant seeds can be processed into high quality vegetable or essential oils, the remaining portion may find various profitable applications due to their phytochemicals content and antioxidant activity. These byproducts can thus be seen as economically promising raw materials for future applications in industrial products for pharmaceutics or cosmetics [24].

Various vegetable oils can be applied for the moisturizing, protection and healing of problematic skins. Besides its nutritional benefits, fennel oil has several positive effects on the skin according to its richness in Mono Unsaturated Fatty Acids (MUFAs) and especially petroselinic acid which can resolve some skin problems, such as dryness [25].Actually, oilseeds are easily biodegradable and skin lipid compatible and thus, their using in cream formulas could reduce the use of synthetic oil such as paraffin oil [26].The potential nutritional and functional properties of agrowastes are studied previously such as polyphenols in hemp, flax and canola seed cakes [27], proteins, fibers and other nutrients in Arachis hypogaea seed cakes [28] and antioxidant activity of extracts of *Guizotia abyssinica* and *Rosa damascena* trigintipetala Dieck [28] byproducts. Regarding *F. vulgare* seeds, several quantitative estimations of protein and fiber contents and total phenols and flavonoids contents, as well as their antibacterial and radical scavenging properties have been done [29,30].

Essential oil yield and quality are dependent on many factors such as genetic and environmental conditions as well as sampling [31,32]. Regarding volatile oil ingredients, the identified compounds in this study were in line with the literature data which showed that the main component of sweet fennel is trans anethole (up to 80%) while the fenchone does not exceed 7.5% [33,34]. Polyunsaturated fatty acids/saturated fatty acids (PUFA/SFA) index express the relationship between saturated and polyunsaturated fatty acids content in vegetable oils. It is considered as important parameter for determination of oil nutrition value, PUFA/SFA index higher than 1 reveals oil with high nutritional value [35]. Our overall results regarding oil content and composition are within the range of prior studies where oil content ranged from 12.2 to 22.8% and the amount of petroselinic acid up was to 80% [36-38]. However, many studies emphasized the effect of genetic characteristics and agronomic traits on vegetable oil yield and composition [39] (Hemingway et al., 2015). On the other hand, our results prove also that fennel seed oil is no less important than coriander seed oil in terms of yield and composition as oil yield obtained in previous studies did not exceed 25.1% with 78.2% of petroselinic acid [22,39].

The solid like (Elastic) property dominates over liquid like (Viscous) property in our formulations, it means that all of our samples display solid like property in storage indicating that the sample will only start to flow when influenced by additional external forces and thus a good product stability [40]. This behaviour is typical of many commercial systems since it improves spreading and penetrability of the product on the skin after topical preparations [41]. Regression curves of all of our formulations show that their fluidity is restored shortly after shear stress removal, this thixotropic behaviour indicate that all formulations can show an acceptable spreadility during skin application [42]. The peroxide index is one of the most common parameters used to characterize oxidative rancidity. It is a measure of the concentration of peroxides and hydro peroxides formed in the initial stages of lipid oxidation [43]. Obtained peroxide values were relatively below the maximum limits, revealing a highly stable formulation against oxidation. Peroxide value of formulation B was statically higher than formulation C, this decreasing in peroxide value was expected as fennel essential oil is rich in antioxidants which can react with radicals and thus prevent peroxide formation. The results of the sensory analysis confirmed the positive impact of fennel oils on the cream sensory characteristics [42].

It has been reported that agro industrial by products can be used as a source of phenolic and flavonoids compounds as well as a good source of natural antioxidants [44]. A similar trend is observed in the case of flavonoid content. This may be due to the dissociation of the phenolic compounds in the aromatic water; thus, a low content remains in the residual meal [45] found that the aqueous extract of fennel seeds contains the highest number of phenols [45,46] found a significant difference in the total content of phenols and flavonoids in fennel seeds from different Mediterranean countries. A strong antioxidant activity exhibited by fennel seeds was reported by several previous studies [47]. Such differential scavenging activities can be due to the presence of different types of bioactive compounds especially phenolics in the extracts, to the extraction method but also to the type of used solvent. Gallic acid, caffeic acid, ellagic acid, quercetin and kaempferol are the main phenolic com pounds identified in fennel seed extracts [48,49]. Extracts with high total phenolic and flavonoids content exhibited relatively high antioxidant activity which supports the hypothesis that phenolics and flavonoids contribute significantly to the DPPH radical scavenging capacity of extracts. Such a good correlation was reported by previous studies on several species including Pimpinella barbata and *Coriandrum sativum* and others [28,50-52]. Among all extracts, the highest bactericidal activity was achieved by residual water against *S. aureus* as its MBC value was the lowest [53,54] reported that aqueous extract of fennel seed was the most active among other extracts. This differential antibacterial activity can be related firstly to the characteristics of each bacterial strain, and secondly to the presence of different phytochemicals such as phenols, flavonoids, tannins, alkaloids and others in the seed's residues [55].

The method of distillation significantly affects the yield and qualitative composition of the essential oil [56]. Essential oil composition also varies depending on the maturation stages of the plant [57]. Fennel 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%) [58]. 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 [59]. 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 [60,61]. Trans-anethole (85.63%) is generally the predominant constituent of the oil [62-66], while estragole is found in small amounts (2.87%), and the quantity of Fenchone is <1%. 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 [67] 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 (Aprotosoaie Shahat and fennel oil samples from Egypt also showed trans-anethole, estragole, fenchone and limonene as the major constituents [68].

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 [69]. 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 [70]. Estragole is rapidly metabolized in humans and excreted in urine as 1'-hydroxyestragole [71]. 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 2,058µg/l, while in diluted instant teas they were from 9 to 912µg/l, estragole contents ranged from 251 to 1718µg/l in unpackaged fruits (seeds) [72] 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 [73].

Aqueous Fruit Extract (AE) demonstrates direct and highly significant in vitrinitic oxide scavenging [74] and antioxidant activities [75,76] and improves activities of antioxidant enzymes in trichloroacetic acid-exposed rats [77]. 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 number of total flavonoids [78]. Moderate antioxidant activity of ethanol fruit extract was, however, independent of the total flavonoid content present in the extract [79]. Four coumarins, isolated from the methanol extract, have shown excellent *in vitro* antioxidant and anti-inflammatory activities [80]. Both methanol extract and essential oil also significantly improved activities of antioxidant enzymes and inhibited lipid peroxidation [81-83]. The essential oil with predominant trans-anethole content showed a significantly higher antioxidant activity with low IC50 value [84] and demonstrated *in vitro* antioxidant capacities comparable to that of alpha-tocopherol and butyrate hydroxyl toluene [85].

Essential oil is, however, rapidly auto-oxidized by light, and the rate of its oxidation is reported to be slower in the dark [86]. 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 [20,87]. The length of storage period of aerial parts, however, significantly affects the antioxidant content and antioxidant activity [88]. 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* [89-91]. *In vitro* activity of essential oil against various strains of *S. aureus* and *E. coli*, against *Salmonella enterica*, *Listeria monocytogenes*, *B. cereus*, *Candidaalbicans*, *Aspergillus Niger*, and *Penicillium* spp and synergistic activity with amoxicillin or tetracycline against *E. coli*, *Sarcinalutea* and *B. subtilisstrains* have been reported [92]. The essential oil also exhibited *in vitro* antifungal activity against *C. albicans*, [93] *aspergillus* species [94] and potent activity against dermatophytes *Trichophyton rubrum*, *T. tonsurans*, *T. mentagrophytes* and Micro sporum gypseum, better than the standard antifungal agents, fluconazole and amphotericin by [95,96] reported the essential oil bactericidal against isolates of multi-drug-resistant Acinetobacter baumannii, a gram-negative coccobacillus, increasingly responsible for nosocomial infections. Strains of klebsiella Pneumonia producing Extended-Spectrum Beta-Lactamase (ESBL) enzyme [97]. Moderate activity of methanol extract against 15 strains of Helicobacter pyloriwith an MIC of 50mcg/ml [98], significant activity of hydro-ethanol extract against campylobacter jejuni [99] and against the multidrug resistant. 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 [100]. 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 [101]. Oral administration of essential oil and anethole is also significantly protective against ethanol-induced gastric lesions in rats [102]. Water extract shows reno protective effects in experimental polycystic ovary syndrome in rats [103] and prevents ovariectomy-induced bone loss, reducing both osteoclast differentiation and function [104]. 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 [105]. Oral fruit water extract lowered systolic blood pressure of spontaneously hypertensive rats and increased water, sodium and potassium excretion [106]. 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 [107]. 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 [108]. Benzoate (EB), an ivermectin 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 [109]. Topical application of water fruit extract also significantly reduced intraocular pressure in both normotensive and experimental glaucoma model in rabbits [110].

Joshi et al. [110] 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 reported significant ache and butyrylcholinesterase inhibitory activity of the essential oil, more than any single active component, Mata et al. [111] 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 [112]. 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 [113]. Fennel supplementation in diet protected rats against cyclosporine-nephrotoxicity [114]. and the essential oil potently protected against ccl4-hepatotoxicity in rats [115]. The fruit extract was also reported to exhibit *in vitro* immuno-modulatory Nf kappaB activities [116]. 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 [117]. 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 [118-121] However, patients complained of the odor and unpleasant fennel taste and 16% patients withdrew from one study for this reason [122]. 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 [123]. In another double-blind RCT in women with mild to moderate idiopathic hirsutism, topical application of 3% fennel gel [124] or application of cream containing 2% ethanol fruit extract significantly reduced hair thickness after 24 weeks of treatment compared to placebo [125].

Topical application of 5% and 8% fennel oil-containing aerosol and cream produced 84% and 70% repellence against mosquitoes

after 90 min of exposure, respectively [126]. 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' [127] 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 [128,129]. 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 [130]. Long-term use to relieve gas and to regulate intestinal function in children is also suggested to cause premature thelarche [131]. 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 [132]. Ethanol extract is reported nonlethal and nontoxic to mice up to a single oral dose of 3g/kg [133] and chronic administration of the extract in a dose of 100mg/kg/day for 90 days caused only significant weight gain in male mice. The oral LD50 of the essential oil in rats is reported to be 1.32g/kg [134]. 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 [135]. 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 [136]. Methanol fruit extract also time-dependently inhibited CYP3A4 in human liver microsomes; 5-Methoxypsoralen (5-MOP) has been suggested as responsible for the CYP3A4 inhibitory activity [137-141].

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