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The chemical constituents and pharmacological effects of *Foeniculum vulgare* - A review

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Abstract: As a result of accumulated experience from the past generations, today, all the world's cultures have an extensive knowledge of herbal medicine. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives. This study was designed to highlight the chemical constituents and pharmacological effects of *Foeniculum vulgare*.

Keywords: *Foeniculum vulgare*, chemical constituents, pharmacology, herb, medicinal plant

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I. INTRODUCTION:

As a result of accumulated experience from the past generations, today, all the world's cultures have an extensive knowledge of herbal medicine. Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives[1-30].

Foeniculum vulgare contained saponins, flavonoids, cardiac glycosides, sterols, triterpenes, coumarins, proteins, volatile oils, trace elements and vitamins. It possessed CNS, reproductive, urinary, antidiabetic, antioxidant, anticancer, antimicrobial, cardiovascular, immunological, dermatological and many other pharmacological effects. This study was designed to highlight the chemical constituents and pharmacological effects of *Foeniculum vulgare*.

Plant profile:

Synonyms:

Anethum dulce DC., *Anethum foeniculum* L. , *Anethum minus* Gouan, *Anethum panmori* Roxb., *Anethum panmorium* Roxb. ex Fleming, *Anethum pannorium* Roxb., *Anethum rupestre* Salisb., *Foeniculum azoricum* Mill., *Foeniculum divaricatum* Griseb., *Foeniculum dulce* Mill., *Foeniculum giganteum* Lojac., *Foeniculum officinale* All., *Foeniculum panmorium* (Roxb.) DC., *Foeniculum piperitum* C. Presl, *Foeniculum rigidum*

Brot. ex Steud, *Foeniculum vulgare* var. capillaceum Burnat, *Foeniculum vulgare* subsp. capillaceum (Burnat) Holmboe, *Foeniculum vulgare* var. dulce (Mill.) Batt. & Trab., *Foeniculum vulgare* var. inodorum Maire, *Foeniculum vulgare* subsp. piperitum (C. Presl) Bég. , *Foeniculum vulgare* var. piperitum (C. Presl) Ball, *Foeniculum vulgare* var. sativum C. Presl, *Foeniculum vulgare* subsp. sativum (C Presl) Janch ex Holub, *Ligusticum foeniculum* (L) Roth, Ligusticum foeniculum (L) Crantz, *Meum foeniculum* (L) Spreng, *Selinum foeniculum* E. H. L. Krause, *Seseli foeniculum* Koso-Pol and *Tenoria romana* Schkuhr ex Spreng[31].

Taxonomic classification:

Kingdom: Plantae, **Phylum**: Spermatophyta, **Subphylum**: Angiospermae, **Class**: Magnoliopsida, **Order**: Apiales, **Family**: Apiaceae, **Genus**: Foeniculum, **Species**: *Foeniculum vulgare* [32-33].

Common Names:

Arabic: shmar, shumar, bisbas, razianj, haba helwa; **Brazil:** Endro, erva-doce, funcho; **Chinese:** hui xiang; **Cuba:** hinojo común **English** fenne, common fennel, Florence fennel, Roman fennel, sweet fennel, anise, sweet anise, aniseed, aniseed weed; **French:** aneth doux, fenouil, fenouil commun, fenuil doux; **Germany:** Echter Fenchel, Garten- Fenchel, Gemüsefenchel, Gewürzfenchel, wilder Fenchel; **Hindi**: Badi saunf, Bari saunf, Moti saunf, Saunf, Saumph; **Indonesia:** adas, adas londo, hades; **Iran**: Razianeh, **Italy:** finocchio; **Japan:** ui-kyo; **Laos:** phak s'i; **Malaysia:** adas pedas; **Netherlands:** venkel **Philippines:** anis, haras; **Portuguese:** funcho; **South Africa:** vinkel; **Spanish:** fonol, hinojo; **Sweden:** faenkaal, fänkål; **Thailand:** phakchi-duanha, thian-klaep, yira[33].

Distribution:

It probably originated from southern Europe and the Mediterranean region. It is cultivated throughout much of the world as a spice, medicinal or essential oil plant, or as a vegetable, and has become naturalized in many places. Now it is recorded in **Africa**: (Algeria, Egypt, Libya, Morocco, Tunisia, South Africa); **Asia**: (Georgia, Afghanistan, Iran, Iraq, Palestine, Jordan, Lebanon, Syria, Turkey, Pakistan); **Europe**: (Ukraine, Albania, Bosnia, Herzegovina, Bulgaria, Croatia, Greece, Italy, Montenegro, France, Portugal, Spain, United Kingdom); **Australasia**: (Australia, New Zealand); **Northern America**: (Mexico; United States); **Southern America**: (Brazil, Costa Rica, El Salvador, Guatemala, Honduras, Venezuela, Argentina, Chile, Paraguay, Uruguay)[34-35].

Description:

Foeniculum vulgare is a biennial plant with a thick rootstock, erect, much-branched, smooth, often 1 meter or more in height. Leaves are 2-, 3-, or 4-pinnate and about 20 centimeters long; the segments are filiform and 2 to 4 centimeters long. Umbels are 5 to 10

centimeters in diameter; the rays number: 8 to 15, about 2 to 3 centimeters long, but longer in fruit, each with 20 to 30 pedicelled yellow flowers. Fruit is ridged, very aromatic, oblong or ellipsoid, about 5 millimeters long. Seeds are somewhat dorsally compressed[36-37].

Traditional uses:

Fennel was considered as one of the oldest medicinal plants and culinary herbs. It was used over 4000 years ago. Fennel was used by the ancient Egyptians as a food and medicine, and it was considered a snake bite remedy in ancient China. It was used since ancient times to treat menstrual disorders, dyspepsia, flatulence and cough, and to reduce the griping effect of laxatives[38]. *Foeniculum vulgare* was widely used in traditional Arabian medicine as diuretic, appetizer, and digestive[39]. The fruit, seeds and young leaves were used for flavoring sweets, dishes and dainties. The young leaves, raw or cooked, were used as flavoring. The seeds have an anise-like flavor and used as flavoring. The infused fruits were used as carminative. Roots were employed as purgative. Crushed fruits were inhaled to counter faintness. Infusion of fruit was used for flatulence. Shoots of young plant were used as carminative and in respiratory disorders. Juice of fruit was used to improve eyesight. Decoction was gargled as a breath freshener or applied as an eyewash. Decoction of seeds was used to regulate menses and as diuretic and emmenagogue. Poultice was used to relieve breast swelling in nursing mothers. Infusion of seeds was used for stomatitis, abdominal cramps, colic, flatulence. Fennel water (aqua foeniculi) was used for colic and flatulence in children. Hot infusion of fruit and of roots was used for amenorrhea. Infusion of roots was given for toothaches and postpartum pains. Infusion of seeds was used for flatulence in babies. Infusion of root was also used for urinary disorders. Oil was used for flatulence and intestinal worms. Paste of seeds or fruit were used in cooling drinks for fevers. Seeds also used as stimulant and to enhance libido, to increase breast milk production, for the treatment of venereal diseases, easing childbirth and soothing cough[36].

Parts used: Whole plant, roots, seeds and oil of seed[36].

Physicochemical parameters of the essential oil of fennel fruit:

Moisture %: 3.35- 4.75; Solubility: alcohol, cloroform, carbon tetrachloride, hexane; acid value (mg/KOH/g): 1.5-2.45; Saponofication value (mg/KOH/g): 121.50-145.75; Ester value: 116.00-141.30; Peroxide value (mEq/kg): 5.65-6.45; Iodine value (g/g): 94.25-98.5; Refractive index at 25°C: 1.5465±0.30-1.5575±0.25; Congealing point (16.4oC): 16.4±0.5- 16.7±0.5; Optical rotation (-2.25 ± 0.70 to + 10.25 ± 0.43) - (-2.10 ± 0.36 to + 10.35 ± 0.45) and Specific gravity at 25°C: 0.978±0.035 -0.985±0.032 [40].

Chemical constituents:

The preliminary phytochemical study revealed the presence of saponins, flavonoids, cardiac glycosides, sterols, triterpenes, coumarins and volatile oils [39, 41]. It also contained

protein, fat, minerals, fibre and carbohydrates. The minerals and vitamins identified in *Foeniculum vulgare* were included calcium, potassium, sodium, iron, phosphorus, thiamine, riboflavin and niacin [42].

Triterpenes, flavanoid glycosides, smaller terpenes (monoterpenoids, sesquiterpenoids and diterpenoids) and reducing sugars were isolated from the seeds of *Foeniculum vulgare*[43].

Total phenolic content in organic fennel oil was 262.59 ± 15.5 mg Gallic Acid Equivalents/l[44]. The phenolics identified in the fruit of this plant were neochlorogenic acid (1.40%), chlorogenic acid (2.98%), gallic acid (0.169%), chlorogenic acid (6.873%), caffeic acid (2.960%), *p*-coumaric acid (4.325%), ferulic acid-7-*o*-glucoside (5.223%), quercetin-7-*o*-glucoside (3.219%), ferulic acid (3.555%), 1,5 dicaffeoylquinic acid (4.095%), hesperidin (0.203%), cinnamic acid (0.131%), rosmarinic acid (14.998%), quercetin (17.097%), and apigenin (12.558%)[45]. However, Parejo *et al*., isolated 3- caffeoylquinic acid, 4-caffeoylquinic acid, 1.5-Odicaffeoylquinicacid, rosmarinic acid, eriodictyol-7-Orutinoside, quercetin-3-O-galactoside, kaempferol-3-Orutinoside, kaempferol-3-O-glucoside, hydroxylcinnamic acid derivatives, flavonoid glycosides and flavonoid aglycones from the aqueous extract of fennel fruits [46]. The furocoumarins imperatorin, psoralen, bergapten, xanthotoxin and isopimpinellin were isolated from the methylene chloride extract. The flavonoids isorhamnetin 3-*O*-α-rhamnoside, quercetin and kaempferol were isolated from the ethyl acetate extract, whereas quercetin 3-*O*-rutinoside, kaempferol 3-*O*-rutinoside and quercetin 3-*O*- β-glucoside were isolated from the methanol extract [47].

Nutritional analysis showed that the plant contained moisture:90.21 g, Energy: 31 kcal, Protein: 1.24 g (Essential amino acids: Leucine: 0.63 g, Isoleucine: 0.73 g, Phenylalanine: 0.45 g, Tryptophane: 0.53 g and Non-essential amino acid (Glycine: 0.55 g, Proline: 0.53 g), Total lipid (fat): 0.2 g (Fatty acids, total saturated: 0.09 g, Fatty acids, total monounsaturated: 0.068 g, Fatty acids, total polyunsaturated: 0.169 g), Carbohydrate: 7.3 g, Total dietary fiber: 3.1 g, Sugars: 3.93 g, Minerals (Calcium: 49 mg, Iron: 0.73 mg, Magnesium: 17 mg, Phosphorus: 50 mg, Potassium: 414 mg, Sodium: 52 mg, Zinc: 0.2 mg), Vitamins (Vitamin: 12 mg, Thiamin: 0.01 mg, Riboflavin: 0.032 mg, Niacin: 0.64 mg, Vitamin: 0.047 mg, Folate: 27 µg, Vitamin A: 48 µg Vitamin E: 0.58 mg, Vitamin K: 62.8 µg)[47].

Essential oils were isolated from fennel aerial parts collected in Cape Verde and from a commercial fennel EO of Portugal were analyzed by NMR, GC and GC-MS. trans-Anethole (32 and 30%, respectively), limonene (28 and 18%, respectively) and fenchone (10% in both cases) were the main compounds identified in the essential oils isolated from fennel from Cape Verde and Portugal, respectively[48].

Foeniculum vulgare essential oil from Turkey contained 74.8% (E)-anethole, 11.1% limonene, 4.7% methyl chavicol, 2.5% fenchone and 1.3% α-pinene[49].

Sing *et al*., investigated the chemical components of volatile oil of *Foeniculum vulgare* (from Gorakhpur), they found that the oil contained (%): acetic acid-ethyl ester: trace, 3-Methylbutanal: 0.1, 2-Methylbutanal: trace, Alpha-Thujene: trace, Alpha-Pinene: 0.2, Camphene: trace, Sabinene: trace, Beta-Pinene: 0.2, Myrcene: 0.1, Delta-3-Carene: 0.1, Alpha-Terpinene: trace, p-Cymene: 3.1, Limonene: 3.1, 1,8-Cineole: 0.1, trans-beta-Ocimene: 0.1, Gamma-Terpinene: 2.1, Fenchone: 8.6, Linalool: 1.2, Camphor: 0.3, Beta-Terpineol: trace, Terpinen-4-ol: 0.2, Alpha-Terpineol: 0.2, Methyl chavicol: 4.7, Fenchyl acetate: 0.2, Cuminal: 0.4, cis-Anethole: 0.4, p-Anisaldehyde: 0.5, trans-Anethole: 70.1, Thymol: 0.1, Alpha-Copaene: 0.1, Beta-Caryophyllene: 0.2, Alpha-Humulene: tracea and Delta-Cadinene: trace [(50)].

However, Upadhyay , isolated 36 components from the essential oil of *Foeniculum vulgare* from Gorakhpur, Uttar Pradesh, India. The main constituents of essential oil were identified as 9-octadecenoic acid (18.56%), 8Z)-14-methyl-8-hexadecenal (7.75%), pentad ecanecarboxylic acid (4.25%), o-benzenedicarboxylic acid (14.47%), 1,3,3-trimethyl-2-vinyl-1-cyclohexene (10.77%), 2-methyl-3-oxoestran- 17-yl acetate (5.46%), 1H-benzocycloheptene (10.71). However, the major and minor constituents isolated from Fennel (*Foeniculum vulgare*) essential oil were included (0.71%) Tetradecane, Hexadecane; (2.05%) Ethanone, 1-(4-methyl-3-cyclohexen-1-YL)-1-(4-methyl-3-cyclohexen-1-YL)ethanone, 2-propanone; (3.67%) H-Benzocycloheptene, 2,4a,5,6,7,8,9, 9a-octahydro-3,5,5-trimethyl-9-methylene-, Longifolene; (0.15%) Phenylmethyl ester; (2.25%) cis-(-)-2,4a,5,6,9a-Hexahydro-3,5,5,9-tetramethyl (1H)) benzocycloheptene; (10.71%) 1H-Benzocycloheptene; (0.26%) m-Methyl acetophenone; (0.21%) alpha.-Caryophyllene; (0.14%) 2-Cyclopenten-1-one, 2-hydroxy-3-methyl-Corylon; (0.54%) p-Guaiacol; (0.48%) 2-(4a,8-Dimethyl-2,3,4,4a,5,6-hexahydro-naphthalen-2-yl)-prop-2-en-1-ol; (0.66%) Vetivenene Neoisolongifolene, Aromadendrene; (0.90%) Anthracene, 1,2,3,4,5,6,7,8-octahydro-1-methyl-; (1.74%) 1-Methyl-6-(3-methylbuta-1,3-dienyl)-7-oxabicyclo [4.1.0] heptane; (1.12%) 1-hydroxy-2-methoxy-2-methoxy-4-methylbenzene; (0.26%) 1-(2,3-Dihydroindol-1-yl)-4-phenyl-butan-1,4-dione; (0.26%) 5,5 Dimethyl-3-vinyl cyclohex-2-en-1-one; (0.54%) 2-Methoxy-4-ethylphenol, 1,2-Dimethoxy-4-methylbenzene; (0.37%) Bis(4-methylphenyl) methanedisulfonate; (0.32%) (-)-5-xatricyclo [8.2.0.0(4,6)] Dodecane, Cedran-9-one; (1.22%) 2,2-dimethyl-3-phenylpropanoate; (0.29%) -Methyl-6-(3-methylbuta-1,3-dienyl)-7-oxabicyclo [4.1.0] heptane; (0.45%) 2,7-dimethyloct-7-en-5-yn-4-yl ester; (2.04%) 2-Methyl-6-(4-methyl-1,3-cyclohexadien-1-yl)-2-hepten-4-one; (3.16%) 3-Methyl-2-butenoic acid; 5.46 2-Methyl-3-oxoestran-17-yl acetate; (0.70%) 3,3,6-Trimethyl-1-indanone; (10.77%) 1,3,3-Trimethyl-2-vinyl-1-cyclohexene; (14.47%) o-Benzenedicarboxylic acid; (0.49%) 1-Isopropyl-1,2,3,4-tetrahydroisoquinoline; (0.20%) 3,4-Dimethyl-1,5-cyclooctadiene; (1.84%) 2-hydroxy-1-(hydroxymethyl)ethyl ester; (4.25%) Pentadecanecarboxylic acid; (7.75%) 8Z)-14-Methyl-8-hexadecenal; (18.56%) 9-octadecenoic acid and (1.00%) 2-cis,cis-9,12-Octadecadienyloxyethanol [(51)].

Analyses (GC and GC/MS) of *Foeniculum vulgare* roots and schizocarp (from the city of Niš, Serbia) essential oils and diethyl ether extracts resulted in identification of 89 different components. The most abundant classes of constituents were the phenylpropanoids (69.5-85.5%) and monoterpenoids (11.7-26.9%). The dominant volatile metabolites of schizocarps were fenchone (13.3-18.8%) and (*E*)-anethole (66.1-69.0%). Contrary to that, terpinolene (6.2-6.5%) and dillapiole (71.4-77.5%) were the major volatiles of fennel roots [(52)].

The chemical analysis of the aerial parts and fruits of *Foeniculum vulgare* Mill. subsp. *piperitum* collected from North Western Mediterranean coastal strip near El-Salloum, Egypt showed the presence of the following fatty acids(%): capric acid 2.83 and3.23, undecanoic acid 18.21 and 20.09, lauric acid 2.13 and 2.45,myristic acid 10.51 and 11.20, pentadecanoic acid 1.79 and 2.10, pentadecenoic acid 7.33 and 7.68, pentadecadienoic acid 9.29 and 10.91, palmitic acid 31.51 and 33.47, stearic acid 0.69 and 0.77, oleic acid 1.55 and 0.40, linolieic acid 0.43 and 0, linolenic acid 0.65 and 0.38, arachidic acid 0.76 and 1.31, behenic acid 0 and 0.41, erucic acid 0.87 and 1.33 and tetracosenoic acid 1.89 and 0 respectively. Hydrocarbons and sterols identified in the aerial parts and fruits of *Foeniculum vulgare* (100) were included: *n*-Decane 3.75 and 4.29, *n*-Dodecane 2.16 and 2.84, *n*-Tridecane 0.88 and 0.34, *n*-Pentadecane 0.47 and 1.09, *n*-Hexadecane 0.49 and 0.65, *n*-Heptadecane 1.64 and 1.44, *n*-Octadecane 1.71 and 2.19, *n*-Nonadecane 0 and 1.11, *n*-Eicosane 5.89 and 10.43 *n*-Monocosane 2.72 and 1.88, *n*-Docosane 0.96 and 1.39, *n*-Tricosane 0 and 2.37, *n*-Tetracosane 0.45 and 0.89, *n*-Pentacosane 2.25 and 4.59, *n*-Hexacosane 2.86 and 5.51, *n*-Heptacosane 0.41 and 0.27, *n*-Octacosane 0.37 and 0.44, *n*-Nonacosane 0.79 and 1.76, *n*-Triacontane 0.53 and 1.35, *n*-Monotriacontane 0.48 and 0.89, *n*-Dotriacontane 2.09 and 2.28, *n*-Tetratriacontane 4.52 and 3.34, *n*-Hexatriacontane 10.27 and 0, *n*-Octatriacontane 7.91 and 2.83, *n*-Tetracontane 1.71 and 0.84, Cholesterol 5.52 and 5.95, β-Sitosterol 5.52 and 5.95, Campesterol 3.33 and 4.04 and Stigmasterol 14.86 and19.04 respectively[(47)].

Cultivated and wild growing samples of *Foeniculum vulgare* from R. Macedonia were studied for their volatiles and fatty acid composition. The main essential oil components were: trans-anethole >80%, estragole < 6%, limonene < 6%, anisaldehyde < 1% and 0.5 % fenchone. The dominant fatty acid was (petroselinic and oleic acid) 75.0-82.8%, followed by linoleic acid 10.8-16.2%, palmitic 4.3-6.9%, stearic 1.2-1.7% and myristic acid 0-2.9% [(53)].

Pharmacological effects:

Effects on urinary system:

The ethanolic fruit extract (500 mg/kg dose) showed, statistically, highly significant diuretic effect in rats, that was evident both after 5 ($P<0.0l$) and 24h ($P<0.05$) of its administration. The plant-induced diuresis comparable to that of urea (960 mg/kg) and was

almost double that of the control animal's urine output. The diuresis was not associated with changes in sodium and/or potassium excretion [39].

The diuretic activity of aqueous and 80% methanol extracts of *Foeniculum vulgare* Mill. (Apiaceae) leaf was evaluated in rats using different doses of aqueous or 80% methanol extract (100, 200 and 400 mg/kg) orally. Rats treated with 200 and 400 mg/kg doses of aqueous and 80% methanol extract of *Foeniculum vulgare* showed an increased urine volume ($P<0.001$). However, 100 mg/kg dose of both extracts failed to produce significant increase in 24 h urine volume compared to control groups. Both extracts increased natriuresis, kaliuresis and chloriuresis ($P<0.001$) at the middle and higher doses [54].

CNS effects:

The anxiolytic activity of the essential oil of *Foeniculum vulgare* (50, 100, and 200 and 400 mg/kg) was studied in mice using elevated plus maze (EPM), staircase test (SCT) and open field test (OFT). In EPM test, 100 and 200 mg/kg doses of the essential oil significantly increased percent number of entries and time spent in open arms compared to control. In SCT test, these doses also reduced rearing significantly compared to controls, while only the 200 mg/kg dose significantly increased number of squares crossed at the center in the OFT test [55].

The anxiolytic activity of ethanolic extracts of *Foeniculum vulgare* fruit was evaluated by elevated plus maze, rota rod, open field test, and hole board model in mices. The efficacy of extract (100-200 mg/kg) was compared with standard anxiolytic drugs diazepam (1mg/kg). Extract administered animals showed exploratory behavior with all tests similar to diazepam. The results showed that the extract significantly increased the number of entries and time spent in the open arm in the elevated plus maze apparatus. In open field test, the extract showed significant increase in number of rearings, assisted rearing and number of square crossed [56].

The anxiolytic activity of the crude ethanolic extract of *Foeniculum vulgare* was studied in albino mice by elevated plus-maze model. The extract at doses of 200 mg/kg and 400 mg/kg has been found to possess significant anti-anxiety activity on the tested experimental models. The extract (400 mg/kg) exhibited maximum anti-anxiety effect. At a higher dose the extract showed increase number of entries and time spent in open arm of elevated plus-maze model. The effect produced by the extract was comparable to that of diazepam [57].

The anti-stress and memory-enhancing properties of *Foeniculum vulgare* boiling water extract (50, 100 and 200 mg/kg, orally) were studied in experimental rats. Urinary levels of vanillylmandelic acid (VMA) and ascorbic acid in rats were used to evaluate anti-stress activity. Conditioned avoidance response was measured in normal and scopolamine-induced amnesic rats to study the memory-enhancing effects. Lipid peroxidation inhibition

assay in liver and brain homogenates of rats was used to evaluate antioxidant activity. Daily administration of *Foeniculum vulgare* extract (50, 100 and 200 mg/kg body weight) 1 h prior to induction of stress significantly ($p < 0.05$) altered the stress-induced urinary biochemical levels of VMA from 395.79 ± 11.23 to 347.12 ± 12.28, 311.21 ± 12.48 and 258.86 ± 10.26 µg/kg, respectively, in 24 h, as well as ascorbic acid excretion levels from 65.74 ± 9.42 to 78.59 ± 8.44, 108.41 ± 15.62 and 125.82 ± 16.94 µg/kg within the same period, respectively. These changes occurred in a dose-dependent fashion, and the levels in the control groups were unchanged. The memory deficits induced by scopolamine (1mg/kg, ip) in rats was reversed by *Foeniculum vulgare* dose-dependently. The extract also exhibited potent antioxidant effect by inhibition of lipid peroxidation in both rat liver and brain homogenates to a greater extent than the standard antioxidant, ascorbic acid [(58)].

The antidepressant effect of *Vetiveria zizanioides* and *Foeniculum vulgare* in comparison with antidepressant drug fluoxetine was investigated in depressive behavior in albino rats. Both Forced swimming test and Tail suspension test were used for screening antidepressant effect. The ethanolic extract of *Vetiveria zizanioides* (100mg/kg) and *Foeniculum vulgare* (200mg/kg) together, fluoxetine (10mg/kg) and saline were administered 30 minutes prior to the tests and the immobility period was recorded for 6 minutes. *Vetiveria zizanioides*(100mg/kg) and *Foeniculum vulgare* (200mg/kg) produced significant antidepressant effect by reduction in immobility period as compared to control. But when given both together they were equally effective as fluoxetine (10mg/kg) [(59)].

The antidepressant effects of methanolic extract of *Foeniculum vulgare* fruits (MEFV) was investigated using force swim test in rats (FST), potentiation of norepinephrine (NE) toxicity in mice and haloperidol induce catalepsy (HIC) in mice. The extract of *Foeniculum vulgare* (250 and 500 mg/kg) was administered orally to rats used in FST and 500mg/kg was administered in HIC and in NE toxicity test in mice. The dose of 250mg/kg and 500mg/kg of extract significantly ($P<0.001$) reduced the immobility times in rats, 500 mg/kg showed more potent effect than imipramine (30mg/kg). In NE toxicity model it was observed that MEFV dose not interfere with adrenergic system. A significant ($P<0.001$) reduction in the duration of catalepsy was observed in the MEFV treated group and Fluoxetine group as compared to the haloperidol treated group. In HIC, mice were sacrificed on the seventh day and TBARS, glutathione, nitrite activities were estimated. Monoamine oxidase inhibiting effect and anti-oxidant effect of *Foeniculum vulgare* may be contributing favorably to the antidepressant-like activity [(60)].

The nootropic and anticholinesterase potential of *Foeniculum vulgare* was studied in mice. Methanolic extract of the whole plant of *Foeniculum vulgare* administered for eight successive days ameliorated the amnesic effect of scopolamine (0.4 mg/kg) and aging-induced memory deficits in mice. The passive avoidance paradigm was used as exteroceptive behavioral model for assessing memory. *Foeniculum vulgare* extract increased step-down latency and acetylcholinesterase inhibition in mice significantly. The authors

postulated that *Foeniculum vulgare* can be employed in treatment of cognitive disorders such as dementia and Alzheimer's disease [61].

Gastrointestinal effects:

Both *Foeniculum vulgare* essential oil and anethole (100 mg/kg, orally) provided significant protection toward ethanol induced gastric lesions in rats [62].

The gastric ulcer protective potential of an aqueous suspension of *Foeniculum vulgare* was evaluated against different acute gastric ulcer models, pyloric ligation (Shay), hypothermic restraint stress, indomethacin and by necrotizing agents (80% ethanol, 0.2 M NaOH and 25% NaCl). Pretreatment with *Foeniculum vulgare* suspension, 250 and 500 mg/ kg bw orally (intraperitoneally in Shay rat model) showed a dose-dependent ulcer protective effects in all the models. Furthermore, it offered protection against ethanol-induced depletion of gastric wall mucus, replenished the reduced nonprotein sulfhydryls concentration and modulated malondialdehyde contents in the gastric tissue. Ethanol induced histopathological lesions was reversed by *Foeniculum vulgare* [63].

The anti-ulcerogenic and antioxidant effects of aqueous extracts of *Foeniculum vulgare* (FVE) (75, 150 and 300 mg/kg) was evaluated in ethanol-induced gastric lesions in rats. Pretreatment with FVE significantly reduced ethanol-induced gastric damage. The anti-ulcerogenic effect of FVE was highest in 300 mg/kg group ($P < 0.001$). Pretreatment with FVE also significantly reduced the MDA levels, and significantly increased GSH, nitrite, nitrate, ascorbic acid, retinol and β-carotene levels [64].

The antiulcerogenic property of *Foeniculum vulgare* was evaluated in Wistar albino rats. The aqueous suspension of fennel was given in two doses (250 and 500 mg/kg b w, orally). Gastric acid secretion studies were undertaken using pylorus ligated (Shay) rats. Gastric lesions in the rats were induced by noxious chemicals including ethanol, strong alkalis and indomethacin. The levels of gastric wall mucus (GWM), nonprotein sulfhydryls (NP-SH) and malondialdehyde (MDA) were also measured in the glandular stomach of rats following ethanol administration. The gastric tissue was also examined histologically. In pylorus-ligated Shay rats, the suspension of fennel significantly reduced the basal gastric acid secretion, titratable acid and stomach ulceration (64 %, 39 % and 100 %), respectively. The suspension significantly ($P < 0.001$, $P < 0.01$ and $P < 0.01$) attenuated gastric ulceration induced by necrotizing agents (80 % ethanol, 0.2 mol/l NaOH, 25 % NaCl) respectively and indomethacin was found to be ($P < 0.01$). The cytoprotective and antiulcer effect was further confirmed histologically. Furthermore, the suspension significantly replenished the ethanol-induced depleted levels of GWM ($P < 0.001$), NP-SH ($P < 0.05$) and diminished ($P < 0.01$) (MDA) concentration of the stomach [65].

The anti-colic effectiveness of fennel seed oil emulsion was studied in infantile colic (125 infants, 2 to 12 weeks of age). The use of fennel oil emulsion eliminated colic, according to the Wessel criteria, in 65% (40/62) of infants in the treated group, which was

significantly better than 23.7% (14/59) of infants in the control group (P < 0.01). Side effects were not reported for infants in groups during the trial [66].

Hydro distilled fruit extract of *Foeniculum vulgare* showed prominent antispasmodic activity in acetylcholine induced spasm. Also hydro distilled extract of *Foeniculum vulgare* showed receptor blocking action (antispasmodic) as that of standard agent (atropine) on isolated guinea pig ileum [40].

The laxative effect of a phytotherapic compound containing (*Pimpinella anisum* L., *Foeniculum vulgare* Miller, *Sambucus nigra* L., and Cassia *augustifolia*) was evaluated by a randomized, crossover, placebo-controlled, single-blinded trial included 20 patients with chronic constipation. Half of the subjects were received the phytotherapic compound for 5-day period, whereas the other half received placebo for the same period. Both treatment periods were separated by a 9-day washout period followed by the reverse treatment for another 5-day period. Mean colonic transit time assessed by X ray was 15.7 hours (95%CI 11.1-20.2) in the active treatment period and 42.3 hours (95%CI 33.5-51.1) during the placebo treatment (P < 0.001). Number of evacuations per day increased during the use of active tea from the second day of treatment (P < 0.001). Patient perception of bowel function was improved (P < 0.01), but quality of life did not show significant differences among the study periods. The findings of the randomized controlled trial revealed that the phytotherapic compound exerted laxative effects and was a safe alternative option for the treatment of constipation [67].

Foeniculum vulgare ethanolic fruit extract administration (500 mg/kg) to rats caused a 33% increase of the collected bile volume that was statistically significant (P<0.0l) compared with control values. The bilirubin content in the collected bile was similar in both treated and control groups [39].

Antimicrobial effect:

The antibacterial effects of methanolic extracts of 23 fennel samples were evaluated against many bacterial isolates. The seed extracts of two samples showed moderate to good inhibitory activities (MICs=62.5-125µg/ml) against three bacteria [68].

Crude extracts of *Foeniculum vulgare* seeds was investigated for antimicrobial activity against *Staphylococcus aureus*, *Micrococcus* spp and *Entecococcus* spp. The results showed that the ethanolic extract had greater activity against *Micrococcus* spp. (MIC=250µg/ml) [43].

Antibacterial activity of aqueous and organic *Foeniculum vulgare* seed extracts was assessed against *Enterococcus faecalis*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa, Salmonella typhi*, *Salmonella typhimurium*, *Shigella flexneri*, using agar diffusion assay. Out of the aqueous extracts prepared in three different ways, hot water extract of seeds (prepared at 40°C) gave better inhibition zones as compared to extracts prepared at ambient temperature of water and boiling water. Organic

extracts showed similar results as observed in case of aqueous extracts with some variations. The extracts prepared in hexane and acetone gave relatively better inhibitory zones ranging from 9–30 mm [(69)].

The antimicrobial effect of the methanol, ethanol, diethyl ether, and hexane extracts of seed of *Foeniculum vulgare* was investigated against *Escherichia coli*, *Salmonella typhi*, *Bacillus cereus, Staphylococcus aureus*, *Candida albicans* and *Aspergillus flavus*. Methanolic extract showed more antimicrobial activity than the other extracts. The results indicated that *Bacillus cereus* and *Aspergillus flavus* were the most sensitive microorganisms, showing the largest inhibition zones and the lowest MIC values. The least antimicrobial activity was recorded against *Escherichia coli* [(45)].

The antibacterial activity of aqueous extract of *Foeniculum vulgare* was studied against *E. coli, Klepsiella spp. and Pseudomonas spp*. The aqueous extracts of *Foeniculum vulgare* showed antibacterial activity, it inhibited the coliform and *Klebsiella* spp [(70)].

The essential oils of the fruits of and *Foeniculum vulgare* Miller var. *vulgare* (Miller) were assayed *in vitro* for antibacterial activity against *Escherichia coli* and *Bacillus megaterium*, bacteria routinely used for comparison in the antimicrobial assays, and 27 phytopathogenic bacterial species and two mycopathogenes responsible for cultivated mushroom diseases. A significant antibacterial activity, as determined with the agar diffusion method, was shown by *Foeniculum vulgare* var. *vulgare* oil [(71)].

Essential oil was investigated for its antibacterial and antifungal activity against seven infectious microbial pathogens, *Escherichia coli* (ATCC 25922), *Bacillus cereus* (ATCC 11778), *Lactobacillus acidophilus* (ATCC 53103), *Micrococcus luteus* (ATCC 9341), *Staphylococcus aureus* (ATCC 25923), *Klebsiella pneumoniae* (ATCC 15380) and *Streptococcus pneumoniae* (ATCC 12755), as well as *Aspergillus niger*, *Candida albicans* and *Rhizopus stolonifer*. The *Foeniculum vulgare* essential oil showed the diameter of inhibition zone (DIZ) ranging from 19.4 ± 0.07 - 26.4 ± 0.09 mm at a concentration of 28 µg/disc in all the ten tested strains. The minimum inhibitory concentration (MIC) of essential oil against bacterial and fungal strains was obtained in the range of 7.0 - 56 µg/ml [(51)].

The antibacterial effects of the ethanolic fruit extract were studied against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa* and *Proteus vulgaris.* The plant extract prevented the growth of *Staphylococcus aureus* and *Bacillus subtilis*. The minimum inhibitory concentration was found to be similar for both microorganisms (1 mg/ml). Other tested organisms were not affected at any of the concentrations used [(39)].

The antimicrobial effect of organic and aqueous leaves extracts of *Foeniculum vulgare* was studied against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus hirea*, *Escherichia coli* and *Candida albicans*. All extracts of *Foeniculum vulgare* showed antibacterial activity against all the tested microorganisms. The most significant and active extract, were methanol and ethyl acetate against all the tested

bacteria in comparaison to the hexane and aqueous extracts. On the other hand, the results of antifungal activity of aqueous extract was better than the hexane and dichloromethane extracts against *Candida albicans* (ATCC and CBS) (MIC = 0.78 mg/ ml). It appear that *C. albicans* ATCC was the least susceptible microorganisms to the ethyl acetate extract [(72)].

The antifungal effects of *Foeniculum vulgare* were studied against *Aspergillus niger , Aspergillus flavus* and *Fusarium graminearum*. *Foeniculum vulgare* showed antifungal activity at a dose of 4 µl. Moreover, with the using food poison technique, the volatile oil and extract5both showed good to moderate zone of inhibition [(50)].

The *in vitro* antifungal activity of *Foeniculum vulgare* essential oils was investigated against three *Candida albicans* strains of different origin using disc and well-diffusion and microdilution method, and compared to Nystatine and Fluconazole as standard anti-mycotics. The results indicated that the studied essential oils showed antifungal activity against all the isolates of *C. albicans* (MIC values:0.06mg/ml - 0.23mg/ml) [(73)].

Antiparasitic effects:

The larvicidal activity of the essential oils and its major constituents were evaluated against third instar larvae of *Aedes aegypti* for 24 h. Pure compounds, such as limonene isomers, were also assayed. The lethal concentrations LC_{50}, C_{90} and LC_{99} were determined by probit analysis using mortality rates of bioassays. A 99% mortality of *Ae. aegypti* larvae was estimated at 37.1 and 52.4 µl/l of fennel essential oils from Cape Verde and Portugal, respectively[(48)].

The repellent activity of (+)-fenchone and (E)-9-octadecenoic acid was tested against *Aedes aegypti* females using skin and patch tests in comparison with the commercial repellent agent (N,N-diethylm-toluamide (DEET) and (Z)-9-octadecenoic acid). In a skin test with female mosquitoes. (+)-Fenchone and (Z)-9-octadecenoic acid (0.4mg/cm^2) exhibited moderate repellent activity 30 min after treatment[(74)].

The larvicidal activity of essential oils was investigated against malaria vector, *Anopheles stephensi*. Of oils of three plants, *Foeniculum vulgare* oil was the most effective against *A. stephensi* with LC_{50} and LC_{90} values of 20.10 and 44.51 ppm, respectively[(75)].

The essential oil of the leaves, flowers, and roots of *Foeniculum vulgare* exerted larvicidal activity against fourth-instar larvae of the mosquito *Culex pipiens molestus*. Terpineol and 1,8-cineole content of *Foeniculum vulgare* were the most effective contents against *Culex pipiensmolestus* bites offering complete protection for 1.6 and 2 h, respectively[(76)].

Antidiabetic effect:

The antiglycation properties of methanolic extracts of 23 fennel samples were evaluated in the bovine serum albumin (BSA)/glucose system. The level of glycation, conformational alterations and protein binding to RAGE receptors were assessed by Congo

red binding assay and a brown staining method. Some samples showed high anti-glycative activity[60].

Effect on reproductive system:

The anti-fertility effect of *Foeniculim vulgare* seed extract was studied in male rats. Rat groups were orally administered 1 ml of hydro-alcoholic extract of fennel seed in four doses of 35, 70, 140, and 280 mg/kg/bw daily for 60 days. After the last gavage, the rats were anaesthetised and the caudal part of the right epididymis was used for sperm counting. After fixation of the testes, microscopic sections were prepared and histological changes were evaluated. The number of spermatogonia after doses of 140 and 280 mg/kg and Sertoli cells after a dose of 140 mg/kg decreased significantly as compared with the control group ($P < 0.05$). The number of primary spermatocytes and sperm count decreased significantly in the treated groups (70, 140, and 280 mg/kg) compared to the control group ($P < 0.05$). Furthermore, thickening of the basement membrane, cell apoptosis, and irregular arrangement of the germinal epithelium were observed in the treated groups[77].

The compound anol or anethole, the major active compound of fennel oil, is considered to be an active estrogenic agent due to its structural resemblance to diethylstilbesterol, a synthetic estrogen. The effect of acetone extracts of *Foeniculum vulgare* seeds at different dose levels (50, 150 and 250ug/100gm bw) was investigated on mammary glands and oviducts of castrated rats. The extract was found to increase nucleic acids and protein concentration as well as the organ weights in both tissues. The medium and high doses were very effective. The results confirmed the estrogenic nature of the seed extract[78].

The essential oil of fennel seeds (500, 750, 1000 mg/kg for 30 days) was investigated for its and anti-osteoporotic activities in ovariectomized rat osteoporosis model. The findings (assessed on the basis of bone mineral density and uterine weight) showed that the fennel essential oil has a preventive effect on development of osteoporosis in ovariectomized rats. This protective effect on early post-ovariectomy bone loss was dose dependent and at the dose of 1000 mg/kg, it was even more than estradiol of 0.082 ± 0.008 g cm^2, $P<0.05$)[79].

The clinical efficacy of fennel extract was compared with echinophora-platyloba in the primary dysmenorrhea. The clinical trial was carried out on sixty unmarried students with mild and moderate dysmenorrhea in Shahrekord university of medical sciences. The severity of pain was detected by the visual analogue scale during two cycles before and two cycles after the intervention. There was no significant difference in the mean of dysmenorrhea severity during the two cycles before the intervention between the two groups, but during the two cycles after the intervention, both drugs could reduce the severity of dysmenorrheal pain but fennel extract showed more significant ($P<0.001$) reduction [80].

Antiinflammatory and analgesic effects:

The analgesic and anti-inflammatory action of the ethanolic extracts of *Foeniculum vulgare* (50,100 and 200mgm/kg, ip) was studied in Wistar rats and Swiss Albino mice. Analgesia was studied in Albino rats using formalin test and in Albino mice using writhing test. Anti-inflammatory activity was investigated by carrageenan- induced hind paw edema. The ethanolic extract produced significant ($P<0.001$) dose-dependent inhibition of pain response elicited by acetic acid and formalin tests. It also exerted dose dependent inhibition of edema development in the carrgeenan induced inflammation [(42)].

The antiinflammatory effect of the essential oil of *Foeniculum vulgare* was investigated using the model of carrageenan induced rat paw edema. It showed anti-inflammatory effect comparable to that of etodolac at 0.050 and 0.200 ml/kg doses [(49)].

The effects of *Foeniculum vulgare* extract in reduction of pain and other systemic symptoms accompanying primary dysmenorrhea were studied using double-blind clinical trial carried out on female students [90 (46 cases and 44 controls)] at Shahid Beheshti University, Iran. Five capsules containing 46 mg of *Foeniculum vulgare* and identical placebos were provided to be taken daily by the case and control groups respectively, during the first three days following the onset of dysmenorrheal pain whenever they needed the medications. The severity of pain in the treated group with *Foeniculum vulgare* extract, showed a significant difference ($P<0.001$) in comparison with the placebo group, in addition to significant differences in systemic symptoms [(81)].

The antinociceptive activities of some components of *Foeniculum vulgare* (alpha-pinene, limonene, fenchone, trans-anethol and alpha-copaene) were investigated for analgesic effects in mice using tail-flick tests. The drugs were injected intraperitoneally in doses of 0.05, 0.1 and 0.2 ml/kg. Alpha-pinene and fenchone caused significant reduction in the nociceptive threshold in the tail-flick test, while, other tested compounds showed no significant analgesic effects [(82)].

The methanolic extract of the aerial parts of *Foeniculum vulgare* subsp. *piperitum* exhibited the highest antinociceptive activity at a dose level of 2000 mg/kg, while the activity exhibited by the ethyl acetate extract was at (800 mg/kg). On the other hand, *n*-hexane extract (700 mg/kg) and methylene chloride extract (500 mg/kg) exhibited similar antinociceptive activities, being less than that of acetylsalicylic acid (200 mg/kg). The results also revealed that the extracts under investigation exhibited significant anti-inflammatory activity. The methanolic extract possessed the highest activity, where it significantly decreased the weight of edema induced by carrageenan in the rat paw at dose levels of 1500 and 2000 mg/kg, it exerted a protective effect of 28 and 47%, respectively, compared to the control value, while ibuprofen (35 mg/kg), used as a reference drug, exhibited a protective effect of 52.23 % [(47)].

Crude ethanolic extracts of *Foeniculum vulgare* seeds was investigated for antinociceptive activity. Results showed that the dose of 298 mg/Kg, compared to the

indomethacin pattern, led to a significant reduction in the number of abdominal writhings in the animals [43].

The hot plate method was used to determine the analgesic activity of the plant . *Foeniculum vulgare* ethanolic fruit extract (500 mg/kg, orally) showed a moderate analgesic activity that was significant after 90 (P<0.5) and 150 minutes (P<0.0l) of its administration. The observed analgesia was of higher magnitude at 150min than after 90min. The ethanolic fruit extract similarly showed an antipyretic activity that was evident at 30 and 90 minutes (P<0.0l) but not at 150 minutes[39].

Effect on osteogenesis:

The effects of *Foeniculum vulgare* extract on proliferation and osteogenesis progress were studied in human mesenchymal stem cells. Results of MTT assay and alkaline phosphatase activity revealed that *Foeniculum vulgare* extract, at range of 5 to 50 µg/ml, positively affect cell proliferation and mineralization. The most proliferation and enzyme activity were seen with dose of 5 µg/ml [83].

Bronchodilatory effects:

The bronchodilatory effects of *Foeniculum vulgare* (aqueous and ethanol extracts and essential oil) were examined by using precontracted isolated tracheal chains of guinea pig. The results indicated bronchodilatory effects of ethanol extract and essential oil of *Foeniculum vulgare* which was not due to inhibitory properties of the plant on muscarinic and histamine H_1 and/or an stimulatory effect on β_2-adrenergic receptors [84].

Effect on glucoma:

A single drop application of aqueous extract of *Foeniculum vulgare* was evaluation for oculohypotensive activity in experimental models of glaucoma. The evaluation of oculohypotensive activity of *Foeniculum vulgare* was done in rabbits with normal intraocular pressure (IOP) and with experimentally elevated IOP achieved with water loading and steroid induced glaucoma models. The aqueous seed extract of *Foeniculum vulgare* exhibited 17.49, 21.16 and 22.03% reduction of intraocular pressure (IOP) in normotensive rabbits at 0.3%, 0.6% and 1.2% (w/v) concentrations respectively. The 0.6% concentration was evaluated in acute and chronic models of glaucoma. A maximum mean difference of 31.20% was observed between vehicle treated and extract treated eyes in water loading model, and a maximum mean IOP lowering of 31.29% was observed in steroid induced model of glaucoma [85].

Hepatoprotective and nephroprotective effects:

The potential protective effect of fennel essential oils was studied against carbon tetrachloride (CCl_4) induced fibrosis in rats. Administration of CCl_4 (1.5ml/kg

/kg bw) intrapretoneally (ip) in olive oil (1:7 dilution) for 7 successive weeks resulted in liver damage manifested by significant increase in serum AST, ALT, ALP, decreased total protein and increased triglycerides, total cholesterol, LDL and decreased HDL level. Rats treated orally with essential oil of *Foeniculum vulgare* (Fennel, 200 &400kg/bw) for 7 successive weeks showed a significant protection against induced increase in serum liver enzyme (AST,ALT, ALP), restored total protein level and ameliorate the increased triglycerides, total, cholesterol, LDL and decreased the HDL. These protective effects were further confirmed by histopathological examination [(86)].

The effect of (whey protein) concentrate (WPC) (0.5g/kg/day) or fennel seed extract (FSE) (200mg/ kg/day) was evaluated on paraoxonase-1 activity (PON1) and oxidative stress in liver of tienilic acid (TA) treated rats. TA administration significantly increased ALT and AST, total- and direct bilirubin levels, serum tumor necrosis factor-α and nitric oxide levels. Furthermore, serum PON1, and hepatic reduced glutathione, glutathione-S-transferase and Na^+/K^+-ATPase values were diminished with a significant rise in the level of hepatic lipid peroxidation. Triglycerides, total- and LDL-cholesterol levels were significantly elevated, while HDL-cholesterol was unchanged. The administration of either WPC or FSE to TA-treated animals significantly protected the liver against the injurious effects of tienilic acid. This appeared from the improvement of hepatic functions, atherogenic markers, Na^+/K^+-ATPase activity, endogenous antioxidants and hepatic lipid peroxidation level; WPC showed the strongest protection effect [(87)].

The nephroprotective effects of different oral doses of aqueous extract of *Foeniculum vulgare* seeds 250 mg/kg, *Solanum nigrum* 500 mg/kg fruit and their mixture (of 250 and 500 mg/kg/oral respectively) were studied in gentamicin induced nephrotoxicity in albino rabbits. All the treatments were continued for 21 days. Blood samples were taken from all groups at day 21 to determine serum urea, creatinine, albumin, plasma malondialdehyde and catalase. Histopathological parameters of kidneys were also examined at day 21. Gentamicin induced oxidative stress and caused structural changes in the kidneys. The aqueous extract of *Foeniculum vulgare* seeds, *Solanum nigrum* fruit and their mixture significantly prevented renal damage by normalizing increased levels of renal markers. Mixture of both plants at high doses exhibited the more nephroprotective and antioxidant activities [(88)].

The renoprotective effect of the aqueous extract of *Foeniculum vulgare* (150 mg/kg bw) was studied in experimental PCOS female rats. The mean values of blood urea nitrogen in PCOS rats treated with low dose of extract of *Foeniculum vulgare* and estradiol valerate and non-treated, was significantly ($P<0.05$) increased compared with non-PCOS and PCOS rats treated with high dose of extract of *Foeniculum vulgare*[(89)]. The protective effect of fennel essential oil (250, 500, and 1000 mg/kg/day, for 10 days) as a phytoestrogen source was studied against cisplatin -induced nephrotoxicity in rats. The serum levels of blood urea nitrogen (BUN) and creatinine (Cr), kidney tissue damage

score (KTDS), kidney weight (KW) and body weight changes in CDDP-treated groups increased significantly ($P < 0.05$). Fennel essential oil did not reduce the BUN, Cr, KTDS, KW and body weight. Also, the serum and tissue levels of nitrite were not altered significantly by fennel essential oil [(90)].

Antimutagenic and anticancer effects:

The potential antimutagenic and cancer chemoprevention effects of the hot water crude extract of sweet fennel (*Foeniculum vulgare* Mill.) seeds were evaluated in well known genetic model organisms: mice and Drosophila, using mutagenicity, molecular and biochemical assays. In mice, mitomycin C (MMC) was administered to mice as a positive control alone before and after treatment with 5 or 0.5 mg/Kg bw or in combination with fennel crude extract as acute (24h) and sub acute (5 consecutive days) doses, respectively. Chromosomal aberration assay in mice bone marrow cells revealed slight insignificant effect of fennel extract on aberrant mitosis rate, while it gave remarkable significant reduction of the MMC induced chromosomal aberrations. This effect was found to be dose-dependent. However, random amplified polymorphism of DNA (RAPD) showed clear variation between different classes of treated and non treated animals against MMC treatment, which reflected DNA protective effect of fennel extract. The serum uric acid, urea and creatinine (kidneys function) and liver function (GOT and GPT activities) were slightly affected by MMC, which were improved by the ingestion of fennel extract. In Drosophila, fennel extract significantly decreased the frequency of cholchicine induced aneuploidy and chromosomal aberrations in post and pre-treatments [(91)].

The apoptotic activity of crude methanolic *Foeniculum vulgare* leave ethanolic extract was investigated in cervical cancer cell lines (HeLa). The induction of apoptosis was determined by analyzing DNA fragmentation in cervical cancer cells treated with active fraction of crude methanol extract using agarose gel electrophoresis. Fragmentation of the DNA was observed at different plant sample concentrations. Morphological observations were carried out and apoptosis body was observed at 125µg/ml of the extract. *Foeniculum vulgare* induced apoptosis on cervical cancer cell line and inhibited cell proliferation through DNA fragmentation [(92)].

The anticarcinogenic potential of anethole was studied in Ehrlich ascites tumour (EAT) in the paw of Swiss albino mice. The results revealed that anethole increased the survival time, reduce the tumour weight and volume and body weight of the EAT-bearing mice. It caused a significant cytotoxic effect in EAT cells in the paw, reduced the levels of nucleic acids and MDA, and increased NP-SH concentrations. The histopathological changes observed after treatment with anethole were comparable to the standard cytotoxic drug, cyclophosphamide. The results on the frequency of micronuclei and the ratio of polychromatic erythrocytes to normochromatic erythrocytes showed anethole to be mitodepressive and non-clastogenic in the femoral cells of mice [(93)].

Antioxidant effect:

The effects of fennel extract (70% ethanol) at a dose of of 100 and 200 mg/kg for 5 days, interaperitoneally, on serum level of oxidative stress was studied in female mice. Results revealed that fennel extract can decrease the serum level of oxidative factors in female mice; the authors concluded that it can be introduced as a novel medicine for treatment of infertility [(94)].

Many phenolic compounds (3- caffeoylquinic acid, 4-caffeoylquinic acid, 1.5-Odicaffeoylquinicacid, rosmarinic acid, eriodictyol-7-Orutinoside, quercetin-3-O-galactoside, kaempferol-3-Orutinoside, kaempferol-3-O-glucoside, hydroxylcinnamic acid derivatives, flavonoid glycosides and flavonoid aglycones) isolated from the plants were antioxidants [(46)].

The antioxidant value of *Foeniculum vulgare* was evaluated by measuring peroxide and thiobarbituric acid values for oil at fixed time intervals. Both, the volatile oil and extract showed strong antioxidant activity in comparison with butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). In addition, their inhibitory action on linoleic acid system was confirmed by monitoring peroxide accumulation in emulsion during incubation through ferric thiocyanate method [(50)].

The antioxidant activity of fennel oils was measured in terms of hydrogen donating or radical scavenging ability, using the stable radical DPPH. Fennel oil showed radical scavenging ability at all tested concentrations, DPPH % Inhibition 11.24-21.88, $IC_{50:}$ 45.89g/l. Ferric reducing capacity of fennel oil was 0.19-0.37 mmol/l Trolox [(44)].

Dermatological effects:

The response of idiopathic hirsutism to topical *Foeniculum vulgare* extract cream was evaluated clinically in a double blind study. 38 patients were treated with creams containing 1%, 2% of *Foeniculum vulgare* extract and placebo. Hair diameter and rate of growth were evaluated. The efficacy of treatment with the cream containing 2% *Foeniculum vulgare* was better than the cream containing 1% *Foeniculum vulgare* and these two were more potent than placebo. The mean values of hair diameter reduction was 7.8%, 18.3% and -0.5% for patients receiving the creams containing 1%, 2% and 0% (placebo) respectively [(95)].

The effect of fennel topical gel on mild to moderate idiopathic hirsutism was studied by randomized, double-blind, placebo-controlled clinical trial using forty four women with mild to moderate idiopathic hirsutism. The treated group received fennel gel 3% and the control group received placebo. Measurements were performed at zero time and 24 weeks after treatment. Hair thickness was similar between the two groups before intervention. The hair thickness reduced from 97.9±31.5 to 75.6±26.7 micron in patients receiving fennel gel after 24 weeks ($P<0.001$). Four patients complained of itching (3 in treated group) and 4 patients

complained of irritation and itching (3 in treated group). However, these differences were not statistically significant [96].

The wound healing action of aqueous extract of *Foeniculum vulgare* (2% and 7% ointment) was studied in rats using excision wound model. Vaseline was used as control while Mupirocin was used as standard. Post treatment the % wound contraction and wound area was measured on 4^{th}, 8^{th}, 12^{th} and 16^{th} day. The results revealed significant decrease in wound area by ointment of aqueous extract of *Foeniculum vulgare* [97].

Antiallergic effect:

In order to establish the antiallergic effect of fruits of *Foeniculum vulgare*, the inhibitory actions of the fruit on 5-lipoxgenase (5-LOX) and b-hexosaminidase release were evaluated. The 70% ethanol extract considerably inhibited 5-LOX-catalyzed leukotriene production from A23187-induced rat basophilic leukemia (RBL)-1 cells. The IC_{50} was 3.2 mg/ml. From this extract, 12 major compounds including sabinene, fenchone, g-terpinene, a-pinene, limonene, *p*-anisylacetone, *p*-anisylaldehyde, estragole (4-allylanisole), *trans*-anethole, scopoletin, bergapten and umbelliferone were isolated. It was found that several terpene derivatives including g-terpinene and fenchone as well as phenylpropanoid, *trans*-anethole, revealed the considerable inhibitory action of 5-LOX. In particular, the IC_{50} of *trans*-anethole was 51.6 mM. In contrast, ethanol extract and the isolated compounds did not show considerable inhibitory activity on the degranulation reaction of b-hexosaminidase release from antigen-treated RBL-2H3 cells. Ethanol extract and *trans*-anethole showed significant inhibition of arachidonic acid-induced ear edema in mice, by oral administration at doses of 100-400 mg/kg [98].

Cardiovascular effects:

The hypotensive effects of the water extract of *Foeniculum vulgare* were investigated in spontaneously hypertensive rats (SHR) and in normotensive Wistar-Kyoto rats (WKY). Oral administration of *Foeniculum vulgare* extract lowered the systolic blood pressure of SHR but not of WKY. In SHR, *Foeniculum vulgare* treatment increased water, sodium and potassium excretion. Ex vivo as well as *in vitro*. *Foeniculum vulgare* extract inhibited the contractile responses of rat aorta to noradrenaline which blocked by N-nitro-L-arginine [99].

The fennel oil and the main component of the fennel oil (anethole) inhibited arachidonic acid-, collagen-, ADP- and U46619-induced platelet aggregation (IC_{50} from 4 to 147 microg/ml). Anethole also prevented thrombin-induced clot retraction at concentrations similar to fennel oil. The essential oil and anethole, tested in rat aorta with or without endothelium, displayed comparable NO-independent vasorelaxant activity at the same antiplatelet concentrations which have been proved to be free from cytotoxic effects *in vitro*. *In vivo*, both *Foeniculum vulgare* essential oil and anethole orally administered in a subacute

treatment to mice (30 mg/kg/day for 5 days) showed significant antithrombotic activity preventing the paralysis induced by collagen-epinephrine intravenous injection (70% and 83% protection, respectively). At the antithrombotic dosage they were free from prohemorrhagic side effect [(62)].

Hypolipidemic effect and effect on body weight:

The effect of *Foeniculum vulgare* fruit extracts in high fat diet and their possible role in obesity and associated cardiovascular disorders were studied in rats. Three fractions prepared by successive solvent technique from methanol extract of *Foeniculum vulgare*. fruits were administered at a dose of 300 mg/bw by oral gavage and volatile oil obtained by hydrodistillation at a dose of 0.2 ml/bw intraperitoneally once daily along with high fat diet to the female albino rats for six weeks. Results revealed that body weight and fat pad weights were reduced in extracts fed animals in a variable pattern. Cholesterol and triglycerides levels, which were elevated in high fat diet fed animals, improved in a significant manner. Maximum activity was observed with methanol fraction of the extracts which contained maximum amount of phenolic (48.37 mg/g) and flavonoidal contents (21.44 mg/g) [(100)].

Toxicity and side effects:

The LD_{50} of *Foeniculum vulgare* essential oil was found to be 1.038 ml/kg [(19)]. However, acute oral toxicity study in female mice revealed that a single high dose (2000 mg/kg) of the essential oil didn't show loss of weight, autonomic behavioral changes or other signs of toxicity. There was also no mortality observed in the study period, suggesting that the LD_{50} (median lethal oral dose) of the essential oil is higher than 2000 mg/kg when given orally [(55)].

The plant extract lethality in mice was tested using three doses (0.5, 1 and 3g/kg, orally). In addition, locomotor activity, bizarre reactions, sensitivity to sound, social interaction, tail posture, aggressive behaviour, ataxia, paralysis, convulsions, tremors, prostration, exophthalmos, pupil size, defaecation, salivation, urination, pattern of respiration, nasal discharge, cyanosis and piloerection was observed over a period of 24 h. The plant extract in doses of 0.5, 1 and 3 g/kg (orally) did not cause any deaths. Only the 3g/kg dose showed signs of reduced locomotor activity and piloerection. Otherwise, all other parameters were negative [(9)]. No restrictions known for the seed used in infusions and preparations containing an equivalent amount of the essential oil. It was not recommended during pregnancy. No restrictions during lactation [(101)].

Dose:

5-7 g per day crushed or ground seeds were used as teas, tea-like products, and other galenical preparations for internal use [(101)].

II. CONCLUSION:

The review highlighted the chemical constituent, pharmacological and therapeutic effects of *Foeniculum vulgare* as promising source of drugs because of its safety and effectiveness.

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