An Insight of Multitudinous and Inveterate Pharmacological Applications of *Foeniculum vulgare* (Fennel)

Fareeduddin Quadri Syed, Muqtadir Baig Mirza, Ayman I. Elkady, Khalid Rehman Hakeem, and Saleh Alkarim

Introduction

Foeniculum vulgare commonly known as fennel belongs to the Apiaceae family. It is a very popular traditional medicinal herb used by humans for a long time (He and Huang 2011). Basically, fennel plant has been originated in the southern Mediterranean region but cultivated throughout the world. Since ancient times Egyptians, Indians, Romans and Chinese cultivated and used fennel in many ways.

Various research studies show that fennel is effective to control viral, bacterial, fungal, mycobacterium and protozoal infections (Badgujar et al. 2014). For the relief of spams and colic due to gas accumulation, gastrointestinal motility, menstruation and lactation fennel was used since earlier time. Antitumour, chemopreventive, hepatoprotective, hypoglycaemic and antihirsutic properties of fennel are reported in many studies (Cioanca et al. 2015). More recent studies suggest that fennel essential oil can be used in controlling anxiety, depression and Alzheimer's disease.

Fennel is used as a seasoning herb. In France and Italy, it is the crucial ingredient in modern cuisine. Being aromatic, all parts are used in cooking. It is used to improve the palatability of meat and fish dishes. And it can be used raw in salads and shakes, as a spice, in herbal teas, as a mouth freshener, etc. (Lim 2013) (Figs. 1, 2, and 3).

Taxonomy

Kingdom: Plantae.
Division: Tracheophyta.
Subdivision: Spermatophytina.

F. Q. Syed (✉) · M. B. Mirza · A. I. Elkady · K. R. Hakeem · S. Alkarim
Department of Biological Science, King Abdulaziz University, Jeddah, Saudi Arabia

© Springer Nature Switzerland AG 2019

M. Ozturk, K. R. Hakeem (eds.), *Plant and Human Health, Volume 3*,
https://doi.org/10.1007/978-3-030-04408-4_11

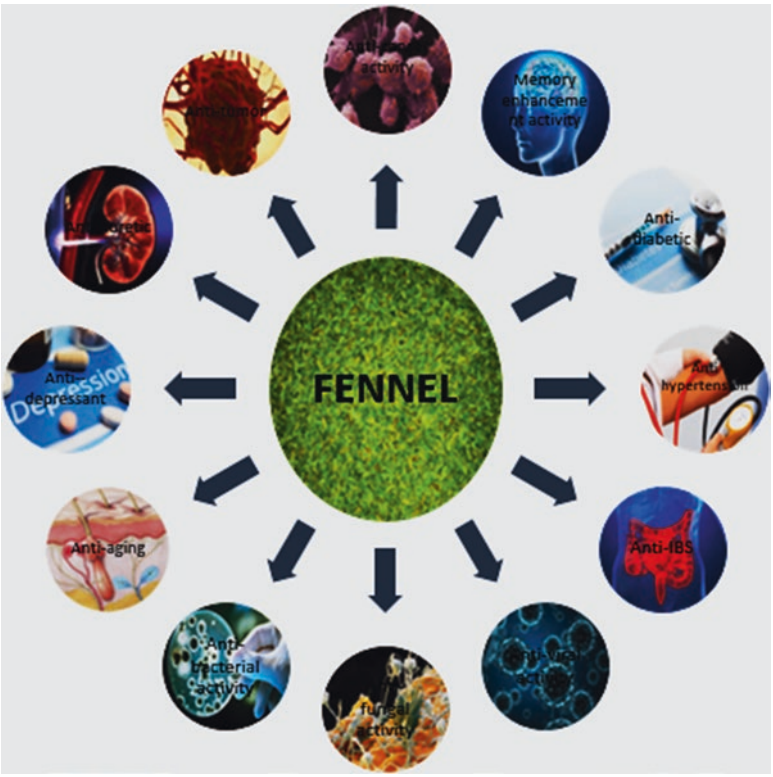

Fig. 1 Multitudinous pharmaceutical applications of fennel

Fig. 2 (**a**) Fennel plant with finely divided foliage. (**b**) Compound umbel with mature flowers. (**c**) Fennel mericarps (seeds)

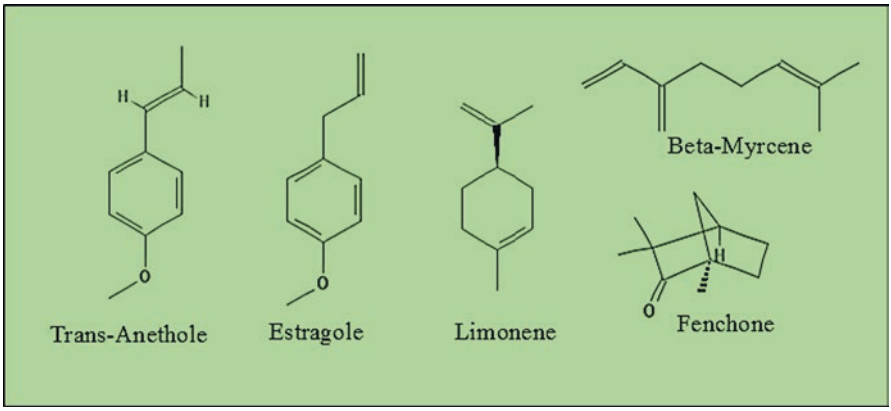

Fig. 3 The molecular structures of the major bioactive essential oil components of fennel

Class: Magnoliopsida.
Subclass: Rosidae.
Order: Apiales.
Family: Apiaceae.
Genus: Foeniculum.
Species: vulgare.

Botanical Description

F. vulgare is a bright green, erect, perennial herb which can grow up to 2 m tall. The foliage is dissected, soft hairy-like dill leaves which cut into fine segments with the length of about 40 cm.

The inflorescence is umbels producing on large branches with thirteen to twenty yellow-colour ray flowers (Barros et al. 2010).

Typically, fennel fruits are greenish yellow, elliptical, elongated shape with vertical ribs over it. The length of the fruit varies from 0.3 cm to 0.5 cm. Fennel can be propagated by root fragments and reproduced by seeds as well.

Nutritional Value of Fennel

Dried *F. vulgare* fruit or seed is the most commonly edible part of the plant. These seeds are commonly referred as fennel. It is sweet and often commercially available in the dried state. According to USDA fennel seeds are rich in sodium, calcium, potassium and phosphorus (Table 1). Besides this, it has abundant fibre and vitamins (USDA 2016).

Table 1 Nutritional value of fennel (USDA 2016)

Nutrient	Per 100 g
Water	8.81 g
Energy	345Kcal
Protein	15.8 g
Total lipid (fat)	14.87 g
Carbohydrate	52.29 g
Fiber, total dietary	39.8 g
Minerals	
Calcium, Ca	1196 mg
Iron, Fe	18.54 mg
Magnesium, Mg	385 mg
Phosphorus, P	487 mg
Potassium, K	1694 mg
Sodium, Na	88 mg
Zinc, Zn	3.7 mg
Vitamins	
Vitamin C, ascorbic acid	21 mg
Thiamin	0.408 mg
Riboflavin	0.353 mg
Niacin	6.05 mg
Vitamin B-6	0.47 mg
Vitamin B-12	0 µg
Vitamin A, RAE	7 µg
Vitamin A, IU	135 IU
Vitamin D (D2 + D3)	0 µg
Vitamin D	0 IU
Lipids	
Fatty acids, total saturated	0.48 g
Fatty acids, total monounsaturated	9.91 g
Fatty acids, total polyunsaturated	1.69 g
Cholesterol	0 mg

Phytochemical Constituents of Fennel

Fennel plant is endorsed by abundant bioactive phytochemicals. Essential oil, flavonoids, phenolic compounds, few secondary metabolites, etc. are accountable for the pharmacological interests.

Essential Oil of Fennel

Essential oils of fennel are the cause of its flavouring properties. Essential oil content varies from geographical variations. Percentage of about 1.1–4.8% essential oil is found in fennel.

Table 2 Fennel essential oil composition (%), obtained by GC–MS (Anwar et al. 2009)

Compound	Composition (%)
Monoterpene hydrocarbons	
Limonene	5.10 ± 0.10
β-Myrcene	0.87 ± 0.10
(z)-β-Ocimene	0.60 ± 0.02
α-Pinene	0.55 ± 0.02
Sabinene	0.19 ± 0.04
α-Phellandrene	0.19 ± 0.02
γ-Terpinene	0.16 ± 0.02
Camphene	0.13 ± 0.03
β-Pinene	0.09 ± 0.02
(z)-β-Ocimene	Trace (<0.05%)
p-Cymene	Trace (<0.05%)
Oxygenated monoterpenes	
Trans-anethole	69.87 ± 0.65
Fenchone	10.23 ± 0.20
Estragole	5.45 ± 0.20
Fenchyl acetate (exo)	0.54 ± 0.10
Fenchyl alcohole	0.40 ± 0.04
Cis-anethole	0.27 ± 0.03
1,8-Cineol	0.23 ± 0.02
p-Anisaldehyde	0.19 ± 0.01
Fenchyl acetate (endo)	0.12 ± 0.03
Sesquiterpene hydrocarbons	
β-Caryophyllene	0.26 ± 0.00
Germacrene D	0.09 ± 0.00

Trans-anethole, methyl chavicol, fenchone and limonene are the prime essential oil components of fennel with the respective percentage of 1.2–88.4%, 0.2–59.1%, 1.1–14.7% and 5.3–15.7% (Bahmani et al. 2016).

Anethole is the most studied compound from fennel. It is an aromatic compound present in the essential oil of fennel. About 70–80% of essential oil of fennel is composed of anethole. It is clear, colourless liquid with very low solubility in water but readily soluble in ethanol. It is 13 times sweeter than sugar having a distinct sweet anise-like flavour (Chen 2014) (Table 2).

Flavonoids and Phenols of Fennel

Apiaceae members are rich in flavonoids and phenols, so as fennel. Farooq Anwar et al. reported that the extract of fennel seeds contains 627.21–967.50 GAE, mg/mL of total phenols, and the total flavonoid content is 374.88–681.96 CE, mg/100 g. Because of their pharmacological importance, various flavonoids and phenols are isolated from fennel (see Table 3).

Table 3 Phenolic compounds in fennel (Parejo et al. 2004)

S. No.	Phenolic compound	S. No.	Phenolic compound
1	p-Hydroxybenzoic acid-O-glucoside	22	3-Caffeoylquinic acid (neochlorogenic acid)
2	5-Caffeoylquinic acid (chlorogenic acid)	23	Esculetin-O-glucoside (esculin)
3	1-Caffeoylquinic acid	24	3-Feruloylquinic acid
4	4-Caffeoylquinic acid (cryptochlorogenic acid)	25	Isorhamnetin-O-dihexoside
5	Isorhamnetin-O-dihexoside	26	6, 8-C-dihexosylapigenin
6	4-Coumaroylquinic acid	27	5-Coumaroylquinic acid
7	5-Feruloylquinic acid	28	Quercetin-O-dihexoside
8	1-Feruloylquinic acid	29	Quercetin-O-dihexoside
9	4-Feruloylquinic acid	30	Quercetin-3-O-rutinoside (rutin)
10	Eriodictyol-7-O-rutinoside (eriocitrin)	31	Luteolin-7-O-rutinoside
11	Quercetin-3-O-galactoside (hyperoside)	32	Naringerin-7-O-rutinoside (narirutin)
12	Quercetin-3-O-glucoside (isoquercitrin)	33	Kaempferol-3-O-rutinoside
13	Kaempferol-3-O-glucoside	34	Isorhamnetin-3-O-rutinoside
14	Quercetin-3-O-glucuronide (miquelianin)	35	Luteolin-7-O-glucuronide
15	Isorhamnetin-3-O-galactoside	36	Isorhamnetin-3-O-glucoside
16	1,3-Dicaffeoylquinic acid	37	Dicaffeoylquinic acid
17	1,5-Dicaffeoylquinic acid	38	Kaempferol-3-O-glucuronide
18	Isorhamnetin-3-O-glucuronide	39	Rosmarinic acid
19	Apigenin-7-O-glucuronide	40	Acacetin-7-O-rutinoside
20	Acacetin	41	Kaempferol
21	Naringenin	42	Isorhamnetin

Pharmacological Importance of Fennel

Foeniculum vulgare has been used since a long time as a remedial herb for many diseases. Many traditional herbal formulations contain fennel as a constituent. Even today fennel is one among the extensively studied plant for its pharmacological importance. Here we compile some of the uses of fennel in various disease, disorders and human well-being (Table 4).

Antibacterial Activity of Fennel

Ample number of studies were carried out for provident evidence for the antibacterial property of fennel and its components. Methanolic extract of fennel seeds and leaf extract from different countries was tested for the antibacterial activity. *Escherichia coli, Staphylococcus aureus, Salmonella typhimurium and Bacillus subtilis* were used in this study to examine the effect of the extract. MICs ranging from 62.5

Table 4 Anti-proliferative and apoptotic activity of fennel on various cancer cell lines

Cell lines	IC50	Fennel extract	References
MCF-7	24.5 ± 0.08 µg/mL	Methanolic extract of fennel seeds	Zaahkouk et al. (2016)
HEPG-2	28.7 ± 0.04 µg/mL		
HCT 116	59.8 ± 0.09 µg/mL		
Hela	129.7 ± 2.05 µg/mL	Acetone extract of aerial parts of fennel	Berrington and Lall (2012)
Vero	85.37 ± 5.26 µ/mL		
MCF-7	5.78 ± 0.59 g/mL	Methanolic extract of fennel seed	Mohamad et al. (2011)
HEPG-2	27.96 ± 0.54 g/mL		
HT-29	41.87 ± 2.72 g/mL		
H460	50.22 ± 3.03 g/mL		
Hela	79.33 ± 3.37 g/mL		
U251	85 ± 2.54 g/mL		
Eol	50 µg/mL	80 % Ethanolic fennel seed extract	Bogucka-Kocka et al. (2008)
C8166	122 µg/mL		
J45	150 µg/mL		
WICL	155 µg/mL		
ML1	300 µg/mL		
H9	300 µg/mL		
1301	300 µg/mL		
HL60	300 µg/mL		
U266	300 µg/mL		
MCF-7	›100	Ethanol extract of fennel	Lall et al. (2015)
HeLa	19.97 ± 0.048		
SNO	›100		
DU145	56.41 ± 0.28		
Vero	›100		
V79	448.00 ± 19.52	Essential oils extracted from leaves of fennel	de Oliveira et al. (2015)
B16F10	112.78 ± 13.74		
MO59J	406.00 ± 1.57		
Normal human dermal fibroblasts (UV irradiation)	Non-efficient (but decrease in the ROS and LDH level)	50 % Ethanolic extract of fennel seeds	Sun et al. (2016)
4 T1	50 µg/mL	80 % Methanolic extract of fennel seeds	Mansourabadi et al. (2015)
MCF-7	69.41 mg/mL	96% of ethanolic extract of fennel fruit	Agustini et al. (2015)
HT29–19(A) HT29-(MS)	~77 µL/mL ~80 µL/mL	Essential oil (commercially available)	Al-Tamimi et al. (2016)
THP-1	No significant effect	Essential oil (commercially available)	Aazzaa et al. (2014)
AGS	25µg/mL	Essential oil	Ghasemi (2015)
L929aA	700 ± 28 µg/mL	100% Methanolic extract of aerial plant parts	Kaileh et al. (2007)
MDA-MB231	500 ± 17 µg/mL		
MCF7	No effect		

to125 μg/mL were observed with the methanolic extract of fennel from various countries (Salami et al. 2016). In another similar study the antimicrobial activity of methanolic extract showed maximum activity of 20 mm inhibition zone against *Staphylococcus aureus,* also showing activity against *Escherichia coli, Bacillus pumilus, Listeria monocytogenes and Enteropathogenic E. coli (EPEC)* (Kumar et al. 2014). Production of cholera toxin (CT) by a various strain of *Vibrio cholerae* was examined under the stress of methanolic extract of fennel seeds. There was a significant inhibitory effect on the production of CT regardless of the strains. The similar inhibitory effect was demonstrated with trans-anethole and 4-allylanisole, essential oil of fennel seeds (Chatterjee et al. 2016). *Helicobacter pylori* are responsible for many gastric problems, peptic ulcers and gastroduodenal cancers. The methanol extract of fennel showed 50 μg/mL MIC to *Helicobacter pylori* (Abdallah 2016). Essential oil of fennel exhibited the antibacterial activity against *Staphylococcus albus, Bacillus subtilis, Salmonella typhimurium, Shigella dysenteriae* and *Escherichia coli*. With the MIC and MBC of 0.125 and 0.25 mg/mL, respectively, *S. dysenteriae* was the most subtle to fennel's essential oil (Diao et al. 2014). Peptides isolated from the fennel seed showed good inhibition in many bacterial strains with the zone of inhibition ranging from 11 to 12.5 mm. When compared with the standard antibiotic chloramphenicol (25 μg), fennel seed peptides have the better activity to most of the strains (Al Akeel et al. 2014). With the MICs ranging from 64 to 256 μg/mL, the fennel oil was found to be active against *Staphylococcus aureus*. With the sublethal concentration, the expression of endotoxins of *S. aureus* was decreased (Qiu et al. 2012). Except for *Klebsiella pneumoniae* and one strain of *Pseudomonas aeruginosa,* both hot water and organic fraction extracts showed substantial antibacterial activity against *Enterococcus faecalis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* 1, *Salmonella typhi*, *Salmonella typhimurium* 1, *S. typhimurium* 2 and *Shigella flexneri.* Ranging from 20 to 80 mg/mL and 5 to 15 mg/mL were the MICs for aqueous and acetone seed extracts, respectively (Kaur and Arora 2009). Essential oils of fennel, anethole and n-hexane extract were tested for the efficacy against the various foodborne bacteria. All these fractions of fennel seeds were found to possess antimicrobial activity (Cetin et al. 2010). Different strains of *Mycobacterium tuberculosis* were used for the testing of anti-mycobacterial activity of twenty compounds isolated from the active fractions of fennel. Among these compounds, 2,4-undecadienal was the most effective with MIC 25–50 μg/mL. Other compounds from fennel with anti-mycobacterial activity are linoleic acid (MIC 100 μg/mL), oleic acid (MIC 100 μg/mL), 1,3-benzenediol (MIC 100–200 μg/mL) and undecanal (MIC 50–200 μg/mL) (Esquivel-Ferriño et al. 2012).

Antiviral Activity of Fennel

Quercetin and isoquercetin are the two flavonoids showing a virostatic effect against *Bluetongue virus* (BTV) in an *in vitro* study. These two compounds were effective on viral growth retardation in BHK cells at a concentration of 0.75 ± 0.11 μM and

1.07 ± 0.17 μM, respectively (Tharanath et al. 2013). Essential oil of fennel exhibited toxicity to *herpes simplex* type-1 (*HSV-1*) and parainfluenza type-3 (PI-3), expressing the cytotoxicity by the cytopathogenic effect. The antiviral activity ranges from 0.8 to 0.025 μg/mL and 1.6 to 0.2 μg/mL, respectively (Erdoğan Orhan et al. 2012). Syncytia formation inhibition assay showed 26.2 ± 11.3% inhibition of HIV-1 fusion by methanol extract of *Foeniculum vulgare* fruit at a concentration of 100 μg/mL (Chang and Woo 2003). Volatile oils of fennel and acetone extract of fennel seeds were effective against papaya ring spot virus with 25–100% of inhibition at various concentrations (Maurya et al. 2005).

Antifungal Activity of Fennel

In a study essential oil of fennel seeds was investigated for antifungal activity against *Trichophyton rubrum, T. tonsurans, T. mentagrophytes* and *Microsporum gypseum*. It was found that the antifungal effect of fennel seeds essential oil was more prominent than the commonly used antifungal fluconazole and amphotericin B (Zeng et al. 2015). A study to evaluate the anti-mycotic effect of essential oil obtained from the seeds and leaves of fennel demonstrates the complete inhibition of mycelial growth of *Alternaria sp., Fusarium oxysporum f. sp. albedinis, Aspergillus brasiliensis* and *Rhizopus stoloniferawas* with the MIC 0.25 μL/mL (Khalid et al. 2015).

Anti-inflammation Effect of Fennel

Scopoletin, 8-methoxypsoralen, bergapten and imperatorin are the four compounds which are isolated from the methylene chloride fraction of fennel fruit that were assessed for the anti-inflammatory and antioxidant effect in macrophages and in mice stimulated by 12-O-tetradecanoylphorbol-13-acetate. All four compounds were found to be effective anti-inflammatory and antioxidant agents. Most effective was imperatorin in both in vivo and in vitro model (Yang et al. 2015). Lipopolysaccharide (LPS)-induced acute lung injury mice model was used in the demonstration of fennel as an anti-inflammatory agent. Fennel reduced the production of inflammatory cytokines interleukin 6 and tumour necrosis factor-alpha. It also reduced pro-inflammatory mediator matrix metalloproteinase 9 and nitric oxide blocking inflammation process effectively (Lee et al. 2015). Methanolic extract of fennel fruit exerts an inhibitory effect on inflammatory diseases and IV allergic reactions in mice (Choi and Hwang 2004). Another study on rodents established that essential oils of fennel have an anti-inflammatory effect comparable to etodolac at 0.05–0.20 mL/kg (Özbek 2005).

Antioxidant Activity of Fennel

Using DPPH method for determination of anti-oxidation capacity G. Angelov and S. Boyadzhieva concluded that extraction of fennel using water as a solvent has high anti-oxidation potential (Angelov 2016). Another study proved that fennel beverage prepared in in-house conditions is an effective antioxidant, measuring >80% anti-oxidation rate by DPPH assay. The anti-oxidation capacity of fennel was comparable to NDGA and Trolox, standard antioxidant compounds (Kontogiorgis et al. 2016). Paraoxonase 1 (PON1), a hydrolase enzyme, was suggested to have a role in the regulation of oxidative stress, fibrosis and hepatic cell apoptosis in chronic liver disease. It has been concluded that fennel seed extract increases the activity of PON1 and mitigates the oxidative stress caused by tienilic acid in mice liver (Abdel-Wahhab et al. 2016). The damage induced by Fenton reaction to the calf thymus DNA was alleviated by fennel seed extract proving fennel as a good source of anti-oxidants in biological systems as well (Goswami and Chatterjee 2014). Antioxidant potential of different parts of fennel plant was used to study the antioxidant potential of each part of the plant. The highest radical scavenging activity and lipid peroxidation inhibition capacity were recorded with the shoots (Barros et al. 2009).

Anti-proliferative and Apoptotic Effect (In Vitro) of Fennel

Samir A.M. Zaahkouk1 et al. reported that methanolic extract of fennel seeds have anti-proliferative effect on MCF-7, HEPG-2 and HCT 116 cells with the IC50 24.5 ± 0.08, 28.7 ± 0.04 and 59.8 ± 0.09 μg/mL (Zaahkouk 2016). Acetone extract of aerial parts of fennel plant shows the growth inhibition of HeLa cells with the IC50 of 129.7 ± 2.05 and to the Vero cells, the IC50 is 85.37 ± 5.26 μg/mL (Berrington and Lall 2012). Methanolic extract of fennel seed shows cytotoxicity to MCF-7, HEPG-2, HT-29, H460, HeLa and U251 with the IC50 (1 g/mL) 15.78 ± 0.59, 27.96 ± 0.54, 41.87 ± 2.72, 50.22 ± 3.03, 79.33 ± 3.37 and 85 ± 2.54, respectively (Mohamad et al. 2011). 80% Ethanolic fennel seed extract shows cytotoxicity to nine human leukaemia cell lines. IC50 (μg/mL) of different cell lines is as follows: Eol 50 μg/mL, C8166 122 μg/mL, J45 150 μg/mL, WICL 155 μg/mL, ML1 300 μg/mL, H9 300 μg/mL, 1301 300 μg/mL, HL60 300 μg/mL and U266 300 μg/mL (Bogucka-Kocka et al. 2008). Effects of ethanol extract of fennel on various cell lines like MCF-7, HeLa, SNO, DU145 and monkey Vero cells were studied and their IC50 was ˃100, 19.97 ± 0.048, ˃100, 56.41 ± 0.28 and ˃100, respectively (Lall et al. 2015). Essential oils extracted from leaves of fennel show the cytotoxicity to V79 (IC50 448.00 ± 19.52), B16F10 (IC50 112.78 ± 13.74) and MO59J (IC50 406.00 ± 1.57) cell lines. In the same study, it was shown that the essential oil of fennel was not effective to HT29, MCF-7, HeLa, HepG2, U343 and U251 cell lines (de Oliveira et al. 2015). 50% Ethanolic extract of fennel seeds was effective against the skin cancer. It decreased the production of ROS and LDH, and enhanced the production

of Nrf and GSH in UV irradiation normal human dermal fibroblasts (Sun et al. 2016). 50 μg/mL of 80% methanolic extract of fennel seeds has shown the best inhibitory effect on mouse breast cancer 4 T1 cell line (Mansourabadi et al. 2015). 96% of ethanolic extract of fennel fruit showed toxicity to MCF-7 cells with the 69.41 mg/mL IC50 (Agustini et al. 2015). Commercially available essential oil of fennel (from city Tulkarm, Palestine) showed apoptotic activity on HT29–19(A) non-muco-secreting and HT29-muco-secreting (MS) cell lines with the IC50 of ~77 μL/mL and ~80 μL/mL, respectively (Al-Tamimi et al. 2016). In a study conducted by Smail Aazza et al. on the anti-proliferative activity of different Moroccan commercial essential oils, THP-1 cells show insignificant effect with fennel essential oils (Aazzaa et al. 2014). The proliferation of AGS cell line of stomach cancer was inhibited by commercially available essential oil of fennel in Iran. The concentration of inhibition of growth of 50% is 25 μg/mL (Ghasemi 2015). With the IC50 values of 700 ± 28 μg/mL and 500 ± 17 μg/mL, the 100% methanolic extract of aerial part of fennel plant showed the anti-proliferative activity on L929aA and MCF-7, respectively. The same extract doesn't show cytotoxicity to MDA-MB231 cell line (Kaileh et al. 2007). Anethole induced apoptosis in MCF-7 and MDA-MB-231 cell lines in ER-independent manner. The study demonstrated the activation of caspase 9 and PARP1/2 cleavage with the increased expression of c-FLIP(s) and p53. There was a suppression in NF-κB in both the cell lines treated with anethole (Chen and DeGraffenried 2012).

Antitumour Activity (In Vivo) of Fennel

UV ray is one of the causes of the skin cancer and hence a study conducted by Zhengwang Sun et al. showed the UV protective effect of fennel on hairless mice. Production of matrix metalloproteinases induced by UV irradiation was inhibited by fennel by inhibiting MAPK signalling pathway and activation of Nrf2 pathway (Sun et al. 2016). Methanolic extract of fennel seed exhibited an antitumour effect in a mouse model of Ehrlich ascites carcinoma tempering lipid peroxidation and enhancing the antioxidants. Fennel extract was cytoprotective by regulating the MDA levels, GSH and catalase activity, against gamma irradiation (Mohamad et al. 2011). B. Singh and R.K. Kale observed the chemopreventive effect of fennel seed for DMBA-induced skin cancer and B(a)P-induced forestomach papilloma genesis in Swiss albino mice. There was a considerable increase in the level of glutathione, glyoxalase I and antioxidant enzyme activity. The peroxidative damage level and lactate dehydrogenase activity were reduced in the treated mice (Singh and Kale 2008).

In one of the studies, a Thai herbal formulation by name Pra-Sa Prao-Yhai with fennel seed as one of a constituent was reported with anticancer activities against cholangiocarcinoma nude mouse xenograft model (Plengsuriyakarn et al. 2012). A study on rats projecting fennel as a chemoprotective against a carcinogen trichloroacetic acid (TCA) concluded that fennel prevented oxidative stress, hence providing evidence of fennel as a chemopreventive and chemoprotective agent (Celik and Isik 2008).

In murine sarcoma-180 transplantable tumour model, combination therapy of cyclophosphamide-anethole was exhibited antitumour activity more than that of anethole alone. But, pretreatment of anethole showed a protective effect on the liver, bone marrow and other organs from the toxicity of cyclophosphamide (Jana et al. 2015).

Antimetastatic Activity

The antimetastatic activity of anethole was elucidated in DU145 cell line. The study suggests that the antimetastatic activity was via regulation of crosstalk between epithelial to mesenchymal transition molecules and matrix metallopeptidases-9 (Ha et al. 2014).

Clinical Trials of Irritable Bowel Syndrome (IBS) and Fennel

Among gastrointestinal disorders, IBS is a frequently diagnosed, one of the most common problems of many throughout the world. Fennel is used for this disorder since a long time. Recent clinical studies show the marvellous effect of fennel for IBS. In a study of 121 patients suffering from IBS, curcumin and fennel essential oil (CU-FEO) capsules were given for 30 days. Symptoms of IBS were prominently reduced with CU-FEO (Portincasa et al. 2016). In another randomised controlled trial, 20 patients with chronic constipation receiving the fennel tea along with other plant products concluded that this tea has laxative efficacy without any adverse effect (Picon et al. 2010).

Anti-diabetes Effect of Fennel

In alloxan-induced diabetic rats, *Foeniculum vulgare* showed a decrease in fasting blood glucose, superoxide dismutase (SOD) and malondialdehyde (MDA) level. A significant increase in the levels of insulin, glutathione-S-transferase (GST), hepatic reduced glutathione (GSH) and catalase is observed (Zaahkouk et al. 2016).

In glucose-loaded mice model methanolic extract of fennel significantly reduced the blood glucose level (Monalisa and Rahmatullah 2015). In vitro evaluation of fennel's phenolic compound was done for the study of antidiabetic effect. It was concluded that the phenolic component from methanolic extract was very effective for diabetes as it inhibited α-amylase and α-glucosidase (Abu-zaiton et al. 2015). In streptozotocin-induced diabetic rats, administration of essential oils at a concentration of 30 mg/kg body weight corrected the hyperglycaemic condition and the activity of serum glutathione peroxidase was also improved. Essential oil of fennel showed positive effects on kidney and pancreas in the pathological studies (El-Soud et al. 2011). In a similar study with the aqueous extract of fennel seeds, comparable

results showed the reduction of hyperglycemic effect in rats (Anitha et al. 2014). Methanolic extract of the whole plant of fennel was also anti-hyperglycemic to diabetic rats. Elevated levels of various enzymes associated with the diabetic were decreased with the administration of the fennel plant extract (Mhaidat et al. 2014).

Hypotensive Effect of Fennel

The water extract of fennel plant was hypotensive when investigated in hypertensive rats. It decreased the systolic blood pressure in hypertensive rats by increasing the excretion of water, sodium and potassium (El Bardai et al. 2001).

Eye Diseases and Fennel

An extensive study conducted on the various plants bearing ophthalmic benefits in Navarra (Spain) has identified fennel as potential phyto-remedy for ophthalmological problems (Calvo and Cavero 2016). Trans-anethole active component of essential of fennel was shown to have an anti-cataract effect. In an in vitro study of cataract, the chicken eye lens was treated with 55 mM glucose to induce cataract. Trans-anethole was effective in reducing cataract by increasing the solubilising lens protein. Besides this, there was a reduced glutathione, SOD and catalase activity. There was also reduction of aldose reductase in the lens treated with anethole. Thus, anethole can be a protective agent of cataract (Dongare et al. 2012).

Water-loaded and steroid-induced glaucoma rabbit model was used to evaluate the oculo-hypotensive activity of fennel. Aqueous extract of fennel showed significant oculo-hypotensive effect (Agarwal et al. 2008).

Osteoporosis Prevention by Fennel

The new bone tissue is produced by osteoblast and the old bone tissue's resorption is done by osteoclasts. The cause of the most adult skeletal disease including osteoporosis is the imbalance in the bone remodelling by osteoblast and osteoclasts. One of the therapeutic approaches to osteoporosis is to inhibit the differentiation of osteoclasts and prevention of bone resorption.

In a study on cultured bone marrow, the aqueous extract of fennel inhibited the osteoclast differentiation and bone resorption. Furthermore, oral administration of fennel to ovariectomy-induced bone loss patients for six weeks has a preventive effect on femoral bone mineral density, bone mineral contact and decreased bone turnover markers. Overall, fennel has a preventive role in postmenopausal osteoporosis (Kim et al. 2012).

Anti-obesity Effect of Fennel

In Korea, a placebo-controlled, single-blinded, randomised study was conducted on overweight women to examine the effect of fennel tea on subjective appetite. Consumption of fennel tea increased the feeling of fullness, decreased hunger and lessened prospective food consumption. Fennel tea might help in appetite control and could reduce the further food consumption in overweight women (Bae et al. 2015)

Hypolipidaemic and Anti-atherogenic Effect of Fennel

Administration of methanolic extract to C57B1/6 mice substantially decreased the plasma lipid levels along with the decrease in the levels of total cholesterol, triglycerides, LDL cholesterol and apolipoproteins. Levels of HDL cholesterol and apolipoprotein were elevated. Histopathology suggested the decrease in the deposition of fat in the liver. The flow of blood in the coronary arteries was facilitated by fennel extract, as it prevented the deposition of lipids (Oulmouden et al. 2014).

The Vasorelaxant Activity of Fennel

Isolated rat aortic ring was used to demonstrate the vasorelaxant effect of fennel. Methylene chloride fraction of the crude methanolic extract holds endothelium-dependent vasorelaxant effect which occurs through the nitric oxide (NO)-3′,5′-cyclic monophosphate pathway (Tettey et al. 2015).

Anxiolytic Activity of Fennel

Adult Swiss albino male mice receiving a various concentration of fennel's essential oil showed decent anxiolytic activity. The activity of fennel's essential oil was comparable to the anxiolytic drug diazepam (Mesfin et al. 2014).

The Anti-depression Activity of Fennel

Methanolic extract of fennel holds noteworthy anti-depression activity. In haloperidol-induced catalepsy mice, the reduction in the duration of catalepsy was observed in the group treated with fennel. Methanolic extract of fennel (500 mg/kg) was more effective than imipramine (30 mg/kg) (Singh et al. 2013).

Fennel and Alzheimer's Disease

In an in vitro study, essential oils and aqueous extracts of aerial parts of fennel plant were reported to have an inhibitory activity of acetylcholinesterase and butyrylcholinesterase. The results were much better than a cholinergic agent, rivastigmine. Fennel could be a potent therapeutic agent in the treatment of Alzheimer's disease (Arantes et al. 2017).

Memory-Enhancing Activity of Fennel

A study on amnesic rats showed the reversing effect of memory loss by fennel. Extract of fennel seeds diminishes scopolamine-induced memory deficit of above 95% over a period of above 12 days (Koppula and Kumar 2013). Another study using a methanolic extract of fennel plant was carried out in amnesic mice model. There was a paradigm shift in learning and remembering ability of scopolamine-induced memory-impaired mice when treated with fennel extract. There was a prominent upsurge in step-down latency and acetylcholinesterase inhibition (Joshi and Parle 2006). Abana, clinically proven cardioprotective herbal formulation containing fennel seed as one of its components, showed the anti-amnesic effect on mice (Parle and Vasudevan 2007).

Cosmetics and Fennel

4% Ethanolic extract of fennel seeds loaded in the emulsion showed a significant effect on skin moisture and transepidermal water loss (TEWL). This study proves fennel as an antiaging agent (Rasul et al. 2012a). Rasul et al. used the same cream for topical application by male volunteers for 3 months. A cream containing fennel extract decreased the skin melanin and sebum content. And also this formulation of fennel possesses anti-erythemic effects. In conclusion, we can say that it is a safe formulation for the treatment of acne and a skin-whitening agent (Rasul et al. 2012b).

Anti-hirsutism Effect of Fennel

A clinical trial carried out in Iran during 2009–2011 on forty-four women with idiopathic hirsutism showed the reduction of the thickness of facial hair by using 3% fennel gel for 6 months (Akha et al. 2014).

The Diuretic Action of Fennel

In a rodent study, hydroalcoholic extract of fennel's dried roots indicates the diuretic effect. The extract administrated to rat showed the increase in urine flow and sodium excretion (Beaux et al. 1997).

The Antithrombotic Activity of Fennel

The potential of anethole as an antithrombotic agent was tested in the guinea pig. Anethole inhibits arachidonic acid, collagens, and ADP- and U46619-induced aggregation. Anethole possesses antiplatelet, clot-destabilising and vasorelaxant activity (Tognolini et al. 2007).

The Bronchodilatory Activity of Fennel

Methacholine-induced contraction of tracheal chains in guinea pig was evidently relieved by essential oil and ethanolic extract of fennel. Bronchodilatory effect of the ethanolic extract was greater than that of diltiazem (Boskabady and Khatami 2003).

Premenstrual Syndrome and Fennel

As it occurs cyclically with various physical and psychological symptoms, the premenstrual syndrome can be clearly identified. In a randomised clinical trial consisting of 48 females of age 16–18, the PMS was reduced significantly in fennel-receiving group for eight weeks (Pazoki et al. 2016).

Dysmenorrhoea and Fennel

Among the gynaecological problems, primary dysmenorrhoea is the most prevalent with the rate of 90% among menstruating women. In a trial of 80 female students given soft capsules of fennel, the intensity of nausea and weakness decreased along with the reduction in the duration of the menstrual period. These findings support the use of fennel as herbal medicine to relieve dysmenorrhea and menstrual duration (Ghodsi and Asltoghiri 2014). A placebo-controlled trial conducted on sixty virgin girls with the complaint of dysmenorrhoea reveals that the fennel is an effective herb to control menstrual pain (Omidvar et al. 2012).

Vaginal Atrophy and Fennel

Among postmenopausal women, vaginal atrophy is one of the major distresses. A double-blind randomised controlled trial conducted on sixty postmenopausal women in Iran concluded that 5% fennel vaginal cream could manage the symptoms of vaginal atrophy effectively in postmenopausal women without any side effects (Yaralizadeh et al. 2016).

Galactagogic Effect of Fennel

Female albino mice were administrated with 100 mg/kg and 200 mg/kg of an ethanolic extract of fennel. The treated group were recorded with the increase in the levels of serum oestrogen, progesterone and prolactin. Prolactin promotes the production of milk (Sadeghpour et al. 2015).

Infantile Colic and Fennel

Administration of fennel extract to infants could treat infantile colic. Fennel extract is beneficial to colic infants. The effect is comparable to the gripe water (Ghazanfarpour et al. 2014).

Anti-ulcer Activity of Fennel

Aqueous extract of fennel has a protective effect against ethanol-induced gastric mucosal lesions in rats. Treatment with fennel extract significantly increased GSH, nitrite, nitrate, ascorbic acid, retinol and β-carotene levels and reduced lipid peroxidation (Birdane et al. 2007).

Hepato-renal Protective Effect of Fennel

Sodium-valproic (SVP) has the toxic effect to liver and kidney. A study on albino rats using sodium-valproic proved the hepato- and renal protective effect of fennel oil. The results show a positive effect of fennel in histopathological examination of liver and kidney besides the encouraging results of biochemical parameters (Al-Amoudi 2017).

Anthelmintic Effect of Fennel

In vitro schistosomicidal activity of essential oil of fennel is moderate against *S. mansoni* worms but has an incredible inhibitory effect on development of eggs (Wakabayashi et al. 2015).

Toxic Effect of Fennel on Pest

Fumigation of essential oil of fennel was toxic to the pest *Tetranychus turkestani* of Iran. It was also toxic to the predator of the pest *O. albidipennis* but to a less extent (Faraji et al. 2016).

Mosquito Larvicidal Effect of Fennel

Essential oil of fennel is a potential remedy to control the vector of dengue, the *Aedes aegypti*. Fennel essential oil displayed prominent larvicidal effect against *Aedes aegypti* (Rocha et al. 2015).

Interaction of Fennel with Drug

Fennel extract was potentially adequate to inhibit all main metabolic pathways regulating the oxidation of acetaminophen (paracetamol) and formation of the hepatotoxic metabolite, NAPQI (N-acetyl-p-benzoquinone imine). The enzyme CYP2E1 is inhibited by fennel with the IC50 value of 23 ± 4 (Langhammer and Nilsen 2014). 5-Methoxypsoralen, a compound isolated from fennel, inhibits CYP3A4 (human liver microsomal cytochrome) by mechanism-based inactivation. The inhibition is time dependent, requiring that NADPH and CYP3A4 activity is recovered by the competitive inhibition (Subehan et al. 2007).

Toxicity

A study on rat embryo limb bud mesenchymal cells suggests that essential oil of fennel reduced the number of stained differentiated foci because of the cell loss. Essential oil of fennel may have a toxic effect on foetal cells without the indication of teratogenicity (Ostad et al. 2004).

Conclusion

Foeniculum vulgare is one of the most commonly used and extensively studied medicinal herbs throughout the world. Multitudinous health benefits are reported by many researchers. Fennel exhibits ethnomedical treatments of chronic health problems like cancer, diabetes, irritable bowl syndrome, dysmenorrhoea and insomnia.

Due to its bioactive constituent fennel shows a diverse range of pharmacological actions which include anti-oxidation, anti-inflammation, anti-pyretic, anti-allergic, antibacterial, antifungal, antiviral, anti-colitic, anti-hirsutism, antistress, anxiolytic, diuretic, etc.

Fennel has chemopreventive, hepatoprotective, anti-ulcer, hypoglycemic, laxative, oestrogenic, hypolipidaemic, memory-enhancing and oculohypotensive properties.

The pharmacological benefits of fennel can be attributed to the phytochemical composition consisting of volatile compounds, flavonoids, phenolic compounds, etc. Minerals and vitamins present in fennel play their own role in making it a multifaceted beneficial herb.

Fennel is extensively studied but mostly in its crude form because of which it is difficult to trace the bioactive compound responsible for attributing particular properties and making the commercial pharmacological application limited. Specific compound-based studies and understanding the mechanism of action could help in bringing the product from lab bench to clinical use.

References

Aazzaa S, Lyoussi B, Megías C, Cortés-Giraldo I, Vioquec J, Figueiredod AC, Miguel MG (2014) Proliferative activities of moroccan commercial essential oils. Nat Prod Commun 9(4):587–594

Abdallah EM (2016) Medicinal plants with antibacterial properties against Helicobacter Pylori: a brief review. iMedPub J 1:13

Abdel-Wahhab KG, Fawzi H, Mannaa FA (2016) Paraoxonase-1 (PON1) inhibition by tienilic acid produces hepatic injury: antioxidant protection by fennel extract and whey protein concentrate. Pathophysiology 23(1):19–25. https://doi.org/10.1016/j.pathophys.2015.10.002

Abu-zaiton A, Alu M, Ali WM (2015) Evaluating the effect of *Foeniculum vulgare* extract on enzymes related with blood pressure and diabetes (in vitro study). Int J Chem Engg Biol Sci 2(2):77–80

Agarwal R et al (2008) Oculohypotensive effects of *Foeniculum vulgare* in experimental models of glaucoma. Indian J Physiol Pharmacol 52(1):77–83

Agustini K et al (2015) Cytotoxic and apoptotic activity on Mcf7 Cell from ethanolic extract of Trigonella Foenum-Graecum L. Aglaia. Indonesian Journal of Cancer Chemoprevention 6(3):78–83

Akha O et al (2014) The effect of fennel (*Foeniculum vulgare*) gel 3% in decreasing hair thickness in idiopathic mild to moderate hirsutism, a randomized placebo controlled clinical trial. Caspian J Intern Med 5(1):26–29

Al Akeel R et al (2014) Evaluation of antibacterial activity of crude protein extracts from seeds of six different medical plants against standard bacterial strains. Saudi J Biol Sci 21(2):147–151. https://doi.org/10.1016/j.sjbs.2013.09.003

Al-Amoudi WM (2017) Protective effects of fennel oil extract against sodium valproate-induced hepatorenal damage in albino rats. Saudi J Biol Sci 24(4):915–924

Al-Tamimi A, Mohammad BR, Abu-Reidah IM (2016) Chemical composition, cytotoxic, apoptotic and antioxidant activities of main commercial essential oils in palestine: a comparative study. Medicines 3(4):27 http://www.mdpi.com/2305-6320/3/4/27

Angelov G (2016) Extraction of fennel (*Foeniculum vulgare*) seeds: process optimization and antioxidant capacity of the extracts. Chem Biochem Eng Q 30(2):245–253 http://silverstripe.fkit.hr/cabeq/assets/Uploads/10-2-16.pdf

Anitha T et al (2014) Antidiabetic activity of the aqueous extracts of *Foeniculum vulgare* on streptozotocin-induced diabetic rats. Int J Adv Pharm Biol Chem 3(2):487–494

Arantes S et al (2017) Antioxidant activity and cholinesterase inhibition studies of four flavouring herbs from alentejo. Nat Prod Res 6419(January):1–5. https://doi.org/10.1080/14786419.2017.1278598

Badgujar SB, Patel VV, Bandivdekar AH (2014) *Foeniculum vulgare* mill: a review of its botany, phytochemistry, pharmacology, contemporary application, and toxicology. Biomed Res Int 2014:32

Bae JY, Kim JE, Choue R, Lim H (2015) Fennel (*Foeniculum vulgare*) and Fenugreek (Trigonella Foenum-Graecum) tea drinking suppresses subjective short-term appetite in overweight women. Clin Nutr Res 4(3):168–174 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4525133&tool=pmcentrez&rendertype=abstract

Bahmani K, Izadi Darbandi A, Faleh Alfekaiki D, Sticklen M (2016) Phytochemical diversity of fennel landraces from various growth types and origins. Agron Res 14(5):1530–1547

Barros L, Heleno SA, Carvalho AM, Ferreira ICFR (2009) Systematic evaluation of the antioxidant potential of different parts of *Foeniculum vulgare* mill from Portugal. Food Chem Toxicol 47(10):2458–2464. https://doi.org/10.1016/j.fct.2009.07.003

Barros L, Carvalho AM, Ferreira ICFR (2010) The nutritional composition of fennel (*Foeniculum vulgare*): shoots, leaves, stems and inflorescences. LWT—Food Sci Technol 43(5):814–818. https://doi.org/10.1016/j.lwt.2010.01.010

Beaux D, Fleurentin J, Mortier F (1997) Diuretic action of hydroalcohol extracts of *Foeniculum vulgare* Var Dulce (D.C.) roots in rats. Phytother Res 11(4):320–322

Berrington D, Lall N (2012) Anticancer activity of certain herbs and spices on the cervical epithelial carcinoma (HeLa) cell line. Evid Based Complement Alternat Med 2012:11

Birdane FM et al (2007) Beneficial effects of *Foeniculum vulgare* on ethanol-induced acute gastric mucosal injury in rats. World J Gastroenterol 13(4):607–611 http://www.wjgnet.com/1007-9327/mcsy.asp

Bogucka-Kocka A, Smolarz HD, Kocki J (2008) Apoptotic activities of ethanol extracts from some Apiaceae on human Leukaemia cell lines. Fitoterapia 79(7–8):487–497 https://doi.org/10.1016/j.fitote.2008.07.002

Boskabady MH, Khatami A (2003) Relaxant effect of *Foeniculum vulgare* on isolated guinea pig tracheal chains. Pharm Biol 41(3):211–215

Calvo MI, Cavero RY (2016) Medicinal plants used for ophthalmological problems in Navarra (Spain). J Ethnopharmacol 190:212–218. https://doi.org/10.1016/j.jep.2016.06.002

Celik I, Isik I (2008) Determination of chemopreventive role of *Foeniculum vulgare* and Salvia Officinalis infusion on Trichloroacetic acid-induced increased serum marker enzymes lipid peroxidation and antioxidative defense systems in rats. Nat Prod Res 22(1):66–75 http://www.ncbi.nlm.nih.gov/pubmed/17999340

Cetin B et al (2010) Antimicrobial activities of essential oil and hexane extract of florence fennel [*Foeniculum vulgare* Var. Azoricum (Mill.) Thell.] against foodborne microorganisms. J Med Food 13(1):196–204 http://www.ncbi.nlm.nih.gov/pubmed/20136455

Chang YS, Woo ER (2003) Korean medicinal plants inhibiting to human immunodeficiency virus type 1 (HIV-1) Fusion. Phytother Res 17:426–429

Chatterjee S et al (2016) In vitro inhibition of cholera toxin production in vibrio cholerae by methanol extract of sweet fennel seeds and its components. Jpn J Infect Dis 69(5):384–389 https://www.jstage.jst.go.jp/article/yoken/69/5/69_JJID.2015.421/_article

Chen C-y (2014) Review on the pharmacological activities of anethole. 5(4):289–292
Chen CH, DeGraffenried LA (2012) Anethole suppressed cell survival and induced apoptosis in human breast cancer cells independent of estrogen receptor status. Phytomedicine 19(8–9):763–767 https://doi.org/10.1016/j.phymed.2012.02.017
Choi EM, Hwang JK (2004) Anti-inflammatory, analgesic and antioxidant activities of the fruit of *Foeniculum vulgare*. Fitoterapia 75(6):557–565
Cioanca O et al (2015) Essential oils from Apiaceae as valuable resources in neurological disorders: Foeniculi vulgare aetheroleum. Ind Crop Prod 88:51–57. https://doi.org/10.1016/j.indcrop.2016.02.064
Diao W-R, Hu Q-P, Zhang H, Jian-Guo X (2014) Chemical composition, antibacterial activity and mechanism of action of essential oil from seeds of fennel (*Foeniculum vulgare* mill.). Food Control 35(1):109–116 http://www.sciencedirect.com/science/article/pii/S0956713513003393
Dongare V, Kulkarni C, Kondawar M, Magdum C (2012) Inhibition of aldose reductase and anticataract action of trans-anethole isolated from *Foeniculum vulgare* mill. fruits. Food Chem 132(1):385–390. https://doi.org/10.1016/j.foodchem.2011.11.005
El Bardai S et al (2001) Pharmacological evidence of hypotensive activity of Marrubium vulgare and *Foeniculum vulgare* in spontaneously hypertensive rat. Clin Exp Hypertens 23(4):329–343
El-Soud NA et al (2011) Antidiabetic activities of *Foeniculum vulgare* mill. essential oil in streptozotocin-induced diabetic rats. Maced J Med Sci 4(2):139–146
Esquivel-Ferriño PC et al (2012) Antimycobacterial activity of constituents from *Foeniculum vulgare* Var. Dulce Grown in Mexico. Molecules 17(7):8471–8482
Faraji N, Seraj AA, Yarahmadi F, Rajabpour A (2016) Contact and fumigant toxicity of *Foeniculum vulgare* and citrus limon essential oils against Tetranychus Turkestani and its predator Orius Albidipennis. J Crop Prot 5(2):283–292
Ghasemi M (2015) Investigation of compositions and effect of herbal essential oils local Silybum Marianum, *Foeniculum vulgare* and Glycyrrhiza Glabra on cell line of stomach cancer by MTT assays in Ardabil, Iran. J Minim Invasive Gynecol 22(6): S166.
Ghazanfarpour M et al (2014) Most common herbal medicines in the treatment of Iranian children: a systematic review most common herbal medicines in the treatment of Iranian children: a systematic review. Int J Pediatr 2:421–425
Ghodsi Z, Asltoghiri M (2014) The effect of fennel on pain quality, symptoms, and menstrual duration in primary dysmenorrhea. J Pediatr Adolesc Gynecol 27(5):283–286. https://doi.org/10.1016/j.jpag.2013.12.003
Goswami N, Chatterjee S (2014) Assessment of free radical scavenging potential and oxidative DNA damage preventive activity of Trachyspermum Ammi L. (Carom) and *Foeniculum vulgare* mill. (Fennel) seed extracts. Biomed Res Int 2014:8
Ha B et al (2014) Regulation of crosstalk between epithelial to mesenchymal transition molecules and MMP-9 mediates the antimetastatic activity of Anethole in DU145 prostate cancer cells. J Nat Prod 77(1):63–69
He W, Huang B (2011) A review of chemistry and bioactivities of a medicinal spice: *Foeniculum vulgare*. J Med Plant Res 5(16):3595–3600
Jana S, Patra K, Mukherjee G (2015) RSC advances antitumor potential of anethole singly and in combination with cyclophosphamide in murine sarcoma-180 transplantable tumor model. RSC Adv 5:56549–56559. https://doi.org/10.1039/C5RA07230A
Joshi H, Parle M (2006) Short communication cholinergic basis of memory-strengthening effect of group. Indian J Pharm Sci 9(3):413–417
Kaileh M et al (2007) Screening of indigenous palestinian medicinal plants for potential anti-inflammatory and cytotoxic activity. J Ethnopharmacol 113(3):510–516
Kaur GJ, Arora DS (2009) Antibacterial and phytochemical screening of Anethum Graveolens Linn., *Foeniculum vulgare* mill. and Trachyspermum Ammi Linn. Indian J Nat Prod Resour 8(6):611
Khalid S et al (2015) Antifungal potential of the seed and leaf *Foeniculum vulgare* mill essential oil in liquid and vapor phase against phytopathogenic fungi. J Appl Pharm Sci 5(11):50–54

Kim TH, Kim HJ, Lee SH, Kim SY (2012) Potent Inhibitory effect of *Foeniculum vulgare* miller extract on osteoclast differentiation and ovariectomy-induced bone loss. Int J Mol Med 29(6):1053–1059

Kontogiorgis C et al (2016) Antioxidant protection: the contribution of proper preparation of Fennel (*Foeniculum vulgare* mill.) beverage. Ind Crop Prod 79:57–62

Koppula S, Kumar H (2013) *Foeniculum vulgare* mill (Umbelliferae) Attenuates stress and improves memory in wister rats. Trop J Pharm Res 12(4):553–558

Kumar MD et al (2014) Phytochemical Investigation and evaluation of antimicrobial and antitubercular activity of Kunstleria Keralensis. World J Pharm Pharm Sc 4(2):465–479

Lall N et al (2015) Natural product research: formerly natural product letters cytotoxicity of syringin and 4- methoxycinnamyl alcohol isolated from *Foeniculum vulgare* on selected human cell lines. Nat Prod Res 29:37–41

Langhammer AJ, Nilsen OG (2014) Fennel and raspberry leaf as possible inhibitors of acetaminophen oxidation. Phytother Res 28(10):1573–1576

Lee HS, Kang P, Kim KY, Seol GH (2015) *Foeniculum vulgare* mill. protects against lipopolysaccharide-induced acute lung injury in mice through ERK-dependent NF-κB activation. Korean J Physiol Pharmacol 19(2):183–189 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4342739&tool=pmcentrez&rendertype=abstract

Lim, T. K. 2013. Edible medicinal and non-medicinal plants. 5: 36–59. http://link.springer.com/10.1007/978-94-007-5628-1

Mansourabadi AH et al (2015) Effects of fennel, asafetida and ginseng ethanolic extracts on growth and proliferation of mouse breast cancer 4T1 cell lines. Adv Herbal Med 1(2):34–39

Maurya S et al (2005) Antiviral activity of essential oils and acetone extracts of medicinal plants against papaya ring spot virus. J Essent Oil Bear Plants 8(3):233–238 http://www.tandfonline.com/doi/abs/10.1080/0972060X.2005.10643452

Mesfin M, Asres K, Shibeshi W (2014) Evaluation of anxiolytic activity of the essential oil of the aerial part of *Foeniculum vulgare* miller in mice. BMC Complement Altern Med 14:310 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4156641&tool=pmcentrez&rendertype=abstract

Mhaidat NM et al (2014) Anti-hyperglycemic properties of *Foeniculum vulgare* in streptozotocin induced diabetes in rats. Int J Pharmacol 11(1):72–75

Mohamad RH et al (2011) Antioxidant and anticarcinogenic effects of methanolic extract and volatile oil of fennel seeds (*Foeniculum vulgare*). J Med Food 14(9):986–1001 http://www.liebertonline.com/doi/abs/10.1089/jmf.2008.0255

Monalisa MN, Rahmatullah M (2015) Antihyperglycemic, analgesic activity, and acute toxicity studies with methanol extract of *Foeniculum vulgare* seeds. World J Pharm Pharm Sci 4(9):198–206

de Oliveira PF et al (2015) Cytotoxicity screening of essential oils in cancer cell lines. Braz J Pharmacogn 25(2):183–188. https://doi.org/10.1016/j.bjp.2015.02.009

Omidvar S, Esmailzadeh S, Baradaran M, Basirat Z (2012) 11-effect of fennel on pain intensity in dysmenorrhoea: a placebo-controlled trial. Ayu 33(2):311–313 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3611645&tool=pmcentrez&rendertype=abstract

Orhan E, Ilkay BÖ, Kartal M, Kan Y (2012) Antimicrobial and antiviral effects of essential oils from selected Umbelliferae and Labiatae plants and individual essential oil components. Turk J Biol 36(3):239–246

Ostad SN, Khakinegad B, Sabzevari O (2004) Evaluation of the teratogenicity of fennel essential oil (FEO) on the rat embryo limb buds culture. Toxicol In Vitro 18(5):623–627

Oulmouden F et al (2014) Hypolipidemic and anti-atherogenic effect of methanol extract of Fennel (*Foeniculum vulgare*) in hypercholesterolemic mice. Int J Sci Knowledge 3(1):42–52

Özbek H (2005) The anti-inflammatory activity of the *Foeniculum vulgare* L. essential oil and investigation of its median lethal dose in rats and mice. IJP—Int J Pharmacol 1(4):329–331 http://ansijournals.com/3/detail.php?id=1&jid=ijp&theme=3&issueno=159&articleno=55029

Parle M, Vasudevan M (2007) Memory enhancing activity of Abana®: an Indian ayurvedic poly-herbal formulation. J Health Sci 53(1):43–52 http://joi.jlc.jst.go.jp/JST.JSTAGE/jhs/53.43?from=CrossRef

Pazoki H, Bolouri G, Farokhi F, Azerbayjani MA (2016) Comparing the effects of aerobic exercise and *Foeniculum vulgare* on pre-menstrual syndrome. Middle East Fertil Soc J 21(1):61–64. https://doi.org/10.1016/j.mefs.2015.08.002

Picon PD et al (2010) Randomized clinical trial of a phytotherapic compound containing Pimpinella Anisum, *Foeniculum vulgare*, Sambucus nigra, and Cassia augustifolia for chronic constipation. BMC Complement Altern Med 10:17 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2874511&tool=pmcentrez&rendertype=abstract

Plengsuriyakarn T et al (2012) Anticancer activities against Cholangiocarcinoma, toxicity and pharmacological activities of Thai medicinal plants in animal models. BMC Complement Altern Med 12(1):23 http://www.scopus.com/inward/record.url?eid=2-s2.0-84858844417&partnerID=tZOtx3y1

Portincasa P et al (2016) Curcumin and fennel essential oil improve symptoms and quality of life in patients with irritable bowel syndrome. JGLD 25(2):151–157 http://www.ncbi.nlm.nih.gov/pubmed/27308645

Qiu J et al (2012) Chemical composition of fennel essential oil and its impact on Staphylococcus aureus exotoxin production. World J Microbiol Biotechnol 28(4):1399–1405

Rasul A et al (2012a) Formulation development of a cream containing fennel extract: in vivo evaluation for anti-aging effects. Pharmazie 67(1):54–58

Rasul A et al (2012b) Sebumetric and mexametric evaluation of a fennel based cream. Sci Asia 38(3):262–267

Rocha, Diara Kady et al (2015) Larvicidal activity against Aedes Aegypti of *Foeniculum vulgare* essential oils from Portugal and Cape Verde. Nat Prod Commun 10(4): 677–682.

Sadeghpour N et al (2015) Study of *Foeniculum vulgare* (fennel) seed extract effects on serum level of estrogen, progesterone and prolactin in mouse. Crescent J Med Biol Sci 2(1):23–27

Salami M, Rahimmalek M, Ehtemam MH (2016) Inhibitory effect of different fennel (*Foeniculum vulgare*) samples and their phenolic compounds on formation of advanced glycation products and comparison of antimicrobial and antioxidant activities. Food Chem 213:196–205. https://doi.org/10.1016/j.foodchem.2016.06.070

Singh B, Kale RK (2008) Chemomodulatory action of *Foeniculum vulgare* (fennel) on skin and forestomach papillomagenesis, enzymes associated with xenobiotic metabolism and antioxidant status in murine model system. Food Chem Toxicol 46(12):3842–3850. https://doi.org/10.1016/j.fct.2008.10.008

Singh JN, Sunil K, Rana AC (2013) Antidepressant activity of methanolic extract of *Foeniculum vulgare* (Fennel) fruits in experimental animal models. J Appl Pharm Sci 3(9):65–70

Subehan, Zaidi SF, Kadota S, Tezuka Y (2007) Inhibition on human liver cytochrome P450 3A4 by constituents of fennel (*Foeniculum vulgare*): identification and characterization of a mechanism-based inactivator. J Agric Food Chem 55(25):10162–10167

Sun Z et al (2016) Dietary *Foeniculum vulgare* mill extract attenuated UVB irradiation-induced skin photoaging by activating of Nrf2 and inhibiting MAPK pathways. Phytomedicine 23(12):1273–1284. https://doi.org/10.1016/j.phymed.2016.06.008

Tettey CO, Yang I, Ocloo A, Shin HM (2015) Vasorelaxant and anti-inflammatory activities of the methylene chloride fraction of *Foeniculum vulgare* fruit extract. J Food Biochem 39:1–9

Tharanath V, Peddanna K, Kotaiah Y, Venkataramana D (2013) Flavonoids isolated from *Foeniculum vulgare* (Fennel) have virostatic efficiency against bluetongue virus. Int J Pharm Sci Rev Res 23(1):237–242

Tognolini M et al (2007) Protective effect of *Foeniculum vulgare* essential oil and anethole in an experimental model of thrombosis. Pharmacol Res 56:254–260

USDA. 2016. National nutrient database for standard reference release 28 Slightly Revised May, 2016 Full Report: 1–5

Wakabayashi KAL et al (2015) Anthelmintic effects of the essential oil of fennel (*Foeniculum vulgare* mill., Apiaceae) against Schistosoma Mansoni. Chem Biodivers 12(7):1105–1114

Yang IJ, Lee DU, Shin HM (2015) Anti-inflammatory and antioxidant effects of coumarins isolated from *Foeniculum vulgare* in lipopolysaccharide-stimulated macrophages and 12-O-tetradecanoylphorbol-13-acetate-stimulated mice. Immunopharmacol Immunotoxicol 37(3):308–317 http://www.ncbi.nlm.nih.gov/pubmed/25990850

Yaralizadeh M et al (2016) Effect of *Foeniculum vulgare* (Fennel) vaginal cream on vaginal atrophy in postmenopausal women: a double-blind randomized placebo-controlled trial. Maturitas 84:75–80

Zaahkouk SAM (2016) Anti carcinogenic activity of methanolic extract of fennel seeds (*Foeniculum vulgare*) against breast, colon, and liver cancer cells. Int J Adv Res 3:1525–1537

Zaahkouk SAM, Ibrahim DF, Elarabi BE (2016) Antioxidants and hypoglycemic studies on Egyptian propolis and *Foeniculum vulgare* on alloxan induced diabetic rats. Int J Animal Biol 2(1):1–10

Zeng H, Chen X, Liang J (2015) In vitro antifungal activity and mechanism of essential oil from fennel (*Foeniculum vulgare* L.) on dermatophyte species. J Med Microbiol 64(1):93–103