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OVERVIEW OF TRADITIONAL USE, PHYTOCHEMICAL AND PHARMACOLOGICAL ACTIVITIES OF FENNEL (FOENICULUM VULGARE)

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ABSTRACT

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*Corresponding Author Harrizul Rivai Faculty of Pharmacy, Andalas University, Limau Manih Campus, Padang 25163, Indonesia. *Foeniculum vulgare* is commonly known as fennel. *Foeniculum vulgare* is a medicinal plant used for the treatment of various diseases. Therefore, it is necessary to find information about this plant's traditional uses, phytochemicals, and pharmacological activities. Information searches were performed using Google Scholar using the keywords "*Foeniculum vulgare*," "fennel," "traditional uses," "phytochemical," and "pharmacological activity." The results show that, in traditional medicine, fennel has been many traditional uses in the treatment of various diseases, such as cancer, fever, abdominal pains, flatulence, gastralgia, gastritis, insomnia, liver pain, mouth ulcer, stomachache, and others. Fennel seeds have been shown a potential drug for the treatment of hypertension. The main components of *F. vulgare* seed essential oil, such as anethole, estragole, and fenchone. The researchers showed several pharmacological activities in these plants, such as antimicrobial, antidiabetic, antihepatotoxic, antithrombotic, antioxidant, antifungal, cardiovascular, and anticancer. The conclusion is that fennel is proven to have a phytochemical component, which can be used as a medicinal ingredient as a phytopharmaca.

KEYWORDS: *Foeniculum vulgare*, fennel, traditional use, phytochemical, pharmacological activity.

INTRODUCTION

Herbal plants always play an essential role in human health and medicine. Natural remedies and herbal medicines are cost-effective methods useful for treating diseases due to low drug side effects compared to chemical drugs. Fennel (*Foeniculum vulgare*) is a hardy, perennial herb with yellow flowers and feathery leaves. It is indigenous to the Mediterranean's shores but has become widely naturalized in many parts of the world, especially on dry soils near the sea-coast and on riverbanks. It is a highly aromatic and flavourful herb used in cooking and, along with the similar-tasting anise, is one of the primary ingredients of absinthe. Florence fennel or finocchio (UK: /fi'npkioo/, US: /-'novk-/, Italian: [fi'npkijo]) is a selection with a swollen, bulblike stem base that is used as a vegetable.^[1]

Fennel (*Foeniculum vulgare*) is a perennial herb. It is erect, glaucous green, and grows to heights of up to 2.5 meters (8 ft), with hollow stems. The leaves grow up to 40 centimeters (16 in) long; they are finely dissected, with the ultimate segments filiform (threadlike), about 0.5 millimeters $\binom{1}{50}$ in) wide. (Its leaves are similar to those of dill but thinner.) The flowers are produced in terminal compound umbels 5–15 centimeters (2–6 in) wide, each umbel section having 20–50 tiny yellow flowers on short pedicels. The fruit is a dry schizocarp

from 4–10 millimeters $(\frac{3}{16}-\frac{3}{8} \text{ in})$ long, half as wide or less, and grooved.^[10] Since the fruit's seed is attached to the pericarp, the whole fruit is often mistakenly called "seed" (Figure 1).^[2]



Foeniculum vulgare is commonly known as fennel and another name in several countries (Table 1). *Foeniculum vulgare* is a medicinal plant used for the treatment of

various diseases. This herb is an aromatic and medicinal herb belonging to the *Umbelliferae* family, originating from the Mediterranean Sea coast and found near river banks. *Foeniculum vulgare* is widely distributed in Argentina, Bulgaria, Germany, Greece, India, and Lebanon.^[3] There are two types of *Foeniculum vulgare*, among them fennel bitter *Foeniculum vulgare* Mill. Subsp. *Vulgare* var. *Vulgare*, and anise *Foeniculum vulgare* subsp. *Vulgare* var. *Dulce*.^[4] *Foeniculum vulgare* can grow to a height of 2.5 m with a hollow stem, and the leaves grow up to a length of 40 cm. The fruit is dry seeds 4–10 mm long.^[5]

Foeniculum vulgare contains saponins, flavonoids, cardiac glycosides, steroids, triterpenes, coumarin, proteins, essential oils, and vitamins.^[6] This plant has different pharmacological properties such as anti-inflammatory, antistress, antioxidant, anti-allergic, analgesic, antibacterial, anticancer, cytotoxicity, etc.^[7] The roots, leaves, and ripe seeds are commonly used for home remedies, especially those related to the digestive system.^[8]

Table 1: Another name of Fennel	(Foeniculum vulga	<i>re</i>) in several	countries. ^[13,14]
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Country	Name
Arabic	Bisbal, razianaj
Brazil	Endro, erva-doce, funcho
Chinese	Hui xiang, xiao hui xiang
English	Bitter fennel, common fennel, sweet fennel, wild fennel
French	Fenouil
Germany	Fenchel, fenchle, bitter fenchel, wilder fenchel, dunkler fenchel
Indonesia	Adas
Italy	Finucchio, finucchiello, finochietto, finocchiella, fenucciu, fenucettu-sarvegu
Japanese	Fenner, uikyou, uikyou, shouikya
Korea	Sohoehyang
Pakistan	Sonef, saunf
Spanish	Hinojo, hinojo amargo, fenoll, fiollo, millua
Swedish	Frankel
Thailand	Phak chi, phak chi duen ha, phak chi lom, thian klaep, yira

In Italy, fennel is used in traditional medicine and spices to aromatize bread, fishes, liqueurs, salads, and cheeses.^[9,11] It is also used as an ingredient in cosmetic and pharmaceutical products. The main components of *F. vulgare* seed essential oil, such as anethole, estragole, and fenchone.^[5-7] The relative concentrations of these compounds vary widely depending on the origin of the fennel.^[12] This review article's objective was to present the existing knowledge of *F. vulgare's* phytochemical composition and reported pharmacological studies.

Scientific classification

Fennel can be classified as follows^[1] Kingdom: Plantae Clade: Tracheophytes Clade: Angiosperms Clade: Eudicots Clade: Asterids Order: Apiales Family: Apiaceae Genus: Foeniculum Species: *F. Vulgare* Binomial name: *Foeniculum vulgare* Mill.

Synonym

- Anethum dulce DC.
- Anethum Foeniculum L.
- Anethum minus Gouan
- Anethum panmori Roxb.

- Anethum panmorium Roxb. ex Fleming
- Anethum piperitum Ucria
- Anethum rupestre Salisb.
- Foeniculum azoricum Mill.
- Foeniculum capillaceum Gilib.
- Foeniculum divaricatum Griseb.
- Foeniculum dulce Mill.
- Foeniculum foeniculum (L.) H.Karst.
- Foeniculum giganteum Lojac.
- Foeniculum officinale All.
- Foeniculum panmorium (Roxb.) DC.
- Foeniculum piperitum C.Presl
- Foeniculum rigidum Brot. ex Steud.
- Ligusticum foeniculum (L.) Roth
- Ligusticum foeniculum (L.) Crantz
- *Meum foeniculum* (L.) Spreng.
- Meum piperitum Schult.
- Ozodia foeniculacea Wight & Arn.
- Selinum foeniculum E.H.L.Krause
- Seseli dulce Koso-Pol.
- Seseli foeniculum Koso-Pol.
- Seseli piperitum Koso-Pol.
- Tenoria romana Schkuhr ex Spreng.

Traditional Uses

Fennel is used as a traditional alternative and balancing medicine in Arabic, Roman, Indian, European, Iranian, and traditional Chinese medicines.^[17,18] The whole part

plant of the fennel can be used medicinally in different forms to treat a variety of diseased conditions. Fennel has been many traditional uses in treating various diseases, such as cancer, fever, abdominal pains, flatulence, gastralgia, gastritis, insomnia, liver pain, mouth ulcer, stomachache, etc. Fennel seeds have been shown a potential drug for the treatment of hypertension.

Foeniculum vulgare Mill. (F. vulgare), commonlyknown as fennel, is a popular medicinal plant with various pharmacological activities mentioned in traditional Iranian medicine (TIM) and modern phytotherapy such as antioxidant, cytotoxic, antiinflammatory, antimicrobial, bronchodilatory, estrogenic, diuretic, lithotriptic, galactagogue, emmenagogue, antithrombotic. hypotensive. gastroprotective, hepatoprotective, memory enhancing, and antimutagenic activities. No serious adverse events were recorded after ingestion of F. vulgare except for some cases of allergic reactions. The estrogenic activity of F. vulgare brings some side effects such as a decrease in protein concentration and acid and alkaline phosphatase in male genital organs, an increase in weight of mammary glands and reproductive organs in women, and premature thelarche in girls. However, no evidence of teratogenicity was recorded. It is better not to use F. vulgare during pregnancy due to its estrogenic activity. Because of cytochrome P450 3A4 (CYP3A4) inhibition, the pharmacokinetic parameters of drugs mainly metabolized by this isozyme may be affected by F. vulgare. Also, a significant interaction between ciprofloxacin and F. vulgare was demonstrated. The current paper aims to review pharmacological properties, toxicity, adverse events, and drug interactions of F. vulgare. It brings conclusive results about the use of this plant in men, women, and during pregnancy.^[17]

On account of its carminative properties, fennel is chiefly used medicinally with purgatives to allay their side effects and, for this purpose, forms one of the ingredients of the well-known compound licorice powder. Fennel water has properties similar to those of anise and dill water: sodium bicarbonate and syrup. These waters constitute the domestic 'gripe water,' used to correct the flatulence of infants. Fennel tea, also employed as a carminative, is made by pouring boiling water on a teaspoonful of bruised fennel seeds. In the Indian Subcontinent, fennel seeds are eaten raw, sometimes with some sweetener to improve eyesight. Extracts of fennel seeds have been shown in animal studies to have potential use in the treatment of glaucoma, as a diuretic and a potential drug for hypertension treatment. It has been used as a galactagogue improving the milk supply of a breastfeeding mother.[18]

PHYTOCHEMICAL REVIEW

Foeniculum vulgare has been reported to contain 6.3% moisture, 9.5% protein, 10% fat, 13.4% minerals, 18.5% fibre, and 42.3% carbohydrates. The minerals and

vitamins present in F. Vulgare are calcium, potassium, sodium, iron, phosphorus, thiamine, riboflavin, niacin, and vitamin C. The molecular structures of the major bioactive essential oil components of Foeniculum vulgare are shown in Figure 2. Molecular structures of some phenols and phenolic glycosides isolated from *Foeniculum vulgare* are shown in Figure 3.^[11] Molecular structures of some flavonoid aglycons reported in Foeniculum vulgare are shown in Figure 4.^[11] Molecular structures of some miscellaneous compounds isolated from Foeniculum vulgare are shown in Figure 5.^[11] A phytochemical test was performed to detect the presence of alkaloids, flavonoids, saponins, steroids, tannins, and triterpenoids Foeniculum vulgare in standard procedures.[19]

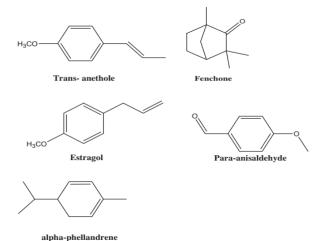
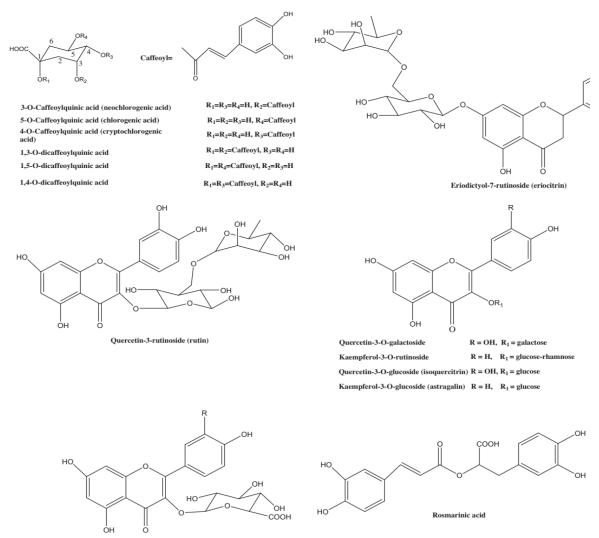


Figure 2: The molecular structures of the major bioactive essential oil components of *Foeniculum vulgare*.^[11]



Quercetin-3-glucuronide, R = OH Kaemferol-3-glucuronide, R = H

Figure 3: Molecular structures of some phenols and phenolic glycosides isolated from *Foeniculum vulgare*.^[11]

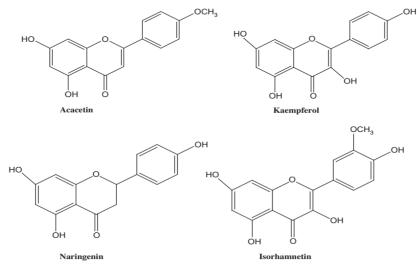


Figure 4: Molecular structures of some flavonoid aglycons reported in *Foeniculum vulgare*.^[11]

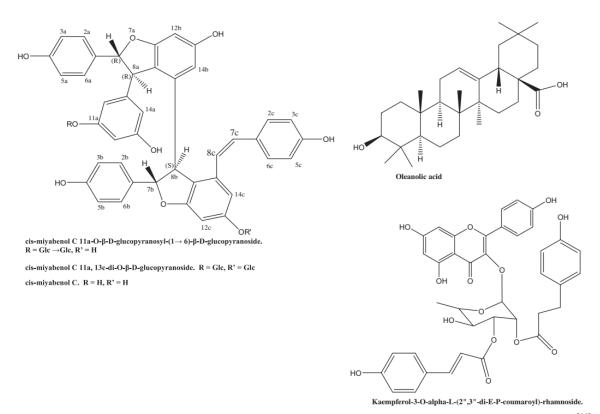


Figure 5: Molecular structures of some miscellaneous compounds isolated from *Foeniculum vulgare*.^[11]

Preliminary phytochemical studies revealed saponins, flavonoids, cardiac glycosides, sterols, triterpenes, coumarins, and essential oils and contained protein, fat, fiber, and carbohydrates. The volatile oil was in fennel seeds. Trans-anethole and fenchone are the main components. α-pinene, camphene, and limonene are also present in essential oils.^[20] Al-Snafi *et al.*, 2018.^[6] report that Foeniculum vulgare essential oil contains 74.8% anethole, 11.1% limonene, 4.7% methyl chavicol, 2.5% fenchone, 1.3% α-pinene. Fennel seed contains 6.3% water, 9.5% protein, 10% fat, 13.4% minerals, 18.5% fibers and 42.3% carbohydrates.^[21] Its leaves contain vitamins and minerals such as calcium, potassium, sodium, iron, phosphorus, thiamine, riboflavin, niacin, and vitamin C. The number of calories was 370. The main ingredients of fennel are anethole (40-70%), (2-9%).[22] fenchone (1-20%),and estragole Identification using GC-MS obtained 29 components of essential oil with a total oil composition of 98.96%. The most FSEO components were trans-anethole (63.30%), pinene (11.11%), and fenchone (8.32%). Some other components such as 2, 3- cyclohexene-1-methanol (2.58%), apiole (2.01%), 3-carene (1.44%), 1-methyl-4-(1- methyl ethyl) benzene (1.32%), methyl chavicol (1.28%) and limonene (1.09%) to a lesser extent.^[23]

Pharmacological Activities

Few extracts of Fennel and isolated compounds have been evaluated for several activities, namely, antiaging,^[24] antimicrobial and antioxidant,^[21] antihirsutism,^[25] antitumor,^[26] anti-inflammatory,^[27] antistress,^[28] anticancer,^[29] hypolipidemic and

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antiatherogenic,^[30] anxiolytic,^[31] antimutagenic activities,^[32] etc. But yet very few pharmacological activities have been found significant.

Anti-aging activity

This study aimed to formulate and evaluate the antiaging effects of a topical cream (w/o emulsion) containing Fennel (Foeniculum vulgare) versus its base. A formulation containing 4% concentrated extract of Foeniculum vulgare was developed by entrapping in the inner aqueous phase of w/o emulsion, and the base had no extract. Both the base and formulation were stored under different storage conditions to predict their stability. The formulation and base were evaluated for effect on skin moisture and transepidermal water loss (TEWL). The base showed insignificant while the formulation showed significant effects on skin moisture and TEWL. The parameter volume and surface evaluation of living skin (SELS) parameters SEr, SEsc, SEsm, SEw were also evaluated and showed a significant $(p \le 0.05)$ decline. The texture parameter energy showed a considerable increase proving that the formulation possesses potential anti-aging effects.[24]

Antimicrobial activity

The chemical composition and biological activity of the essential oils obtained from the leaves of two different cultivars of Florence fennel cropped under three other fertilization treatments (Control not fertilized; Mineral Fertilization; Compost from Municipal Solid Wastes) have been analyzed. All the oils were characterized by high anethole concentration, and some also showed a

good percentage of limonene. Thus, the leaves of Florence fennel, agricultural wastes, could be used to recover anethole from being used for its flavoring and biomedical properties. The antimicrobial activity expressed by assays on the examined oils indicates an appreciable effect, generally higher on Gram-positive bacteria. The various samples of Florence fennel analyzed did not show any results with the FRAP test. The DPPH test showed a weak capacity of the models to catch the free radicals from the solution, attributable to their content in anethole.^[21]

Several studies have been conducted to validate the potential of *F. vulgare* as its antimicrobial, antimycobacterial. Dusko *et al.* (2006),^[33] has surveyed 12 medicinal plants. Apiaceae family, including *F. vulgare*, found that these plants have antibacterial effects. Mahdavi *et al.* (2017),^[34] was made ethanol extract from fennel seeds. As a result, the ethanolic extract of fennel seed benefits from appropriate antibacterial and antioxidant properties. It can be used in combination with other preservatives to preserve food against various oxidative systems and microorganisms that cause infection and intoxication.

Anti-hirsutism activity

Idiopathic hirsutism is defined as the occurrence of excessive male pattern hair growth in women who have a normal ovulatory menstrual cycle and normal levels of serum androgens. It may be a disorder of peripheral androgen metabolism. In this study, we evaluated the clinical response of idiopathic hirsutism to topical Fennel extract. Fennel, Foeniculum vulgare, is a plant, which has been used as an estrogenic agent. The ethanolic extract of fennel was obtained by using a soxhlet apparatus. In a double-blind study, 38 patients were treated with creams containing 1%, 2% of Fennel extract, and placebo. Hair diameter was measured, and the rate of growth was considered. The efficacy of treatment with the cream containing 2% Fennel is better than the cream containing 1% Fennel, 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.^[25]

Antitumor activity

This study was designed to examine invitro cytoprotection activity of methanolic extract of Foeniculum vulgare and Helicteres isora against normal human blood lymphocytes by micronucleus assay antitumor activity against B16F10 melanoma cell line by Trypan blue exclusion assay for cell viability. Lymphocyte culture treated with 70% methanolic extract of *Foeniculum vulgare* and 50% methanolic extract of Helicteres isora showed a significantly less percentage of micronucleus, i.e., 0.006% and 0.007%, respectively as compared to standard drug doxorubicin, which led 0.018% micronucleus. On the other hand, 70% methanolic extract of Foeniculum vulgare good

antitumor activity at the concentration of 200μ g/mL, and 50% methanolic extract of *Helicteres isora* displayed good antitumor activity at the concentration of 300 μ g/mL. The results strengthen that the *Foeniculum vulgare* and *Helicteres isora* could be considered a natural resource of antitumor agents and cytoprotective to normal cells.^[26]

Anti-inflammatory activity

Oral administration (200 mg/kg) of *Foeniculum vulgare* fruit methanolic extract exhibited inhibitory effects against acute and subacute inflammatory diseases and type IV allergic reactions and showed a central analgesic effect. Moreover, it significantly increased the plasma superoxide dismutase (SOD) and catalase activities and the high-density lipoprotein cholesterol. On the contrary, the malondialdehyde (MDA) (as a measure of lipid peroxidation) level was significantly decreased in the *F. vulgare* fruit methanolic extract group compared to the control group (P<0.05). These results seem to support the use of *F. vulgare* fruit methanolic extract in relieving inflammation.^[27]

Antistress activity

The study is to evaluate the antistress and memoryenhancing properties of F. Vulgare extract in experimental rats. F. vulgare plant extract was obtained using the Soxhlet extraction technique. At doses of 50, 100, and 200 mg/kg body weight, the extract was administered orally with an orogastric tube. Urinary levels of vanillylmandelic acid (VMA) and ascorbic acid in rats were used to evaluate antistress 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 F. Vulgare extract (50, 100, and 200 mg/kg body weight) 1 h before 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 , $311.21 \pm$ 12.48 and 258.86 \pm 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 also within the same period, respectively. These changes occurred in a dose-dependent fashion, and the levels in the control groups were unchanged within the same period. Dose-dependently, F. vulgare reversed the memory deficits induced by scopolamine (1 mg/kg, i.p.) in rats. The extract also exhibited a potent antioxidant effect by inhibiting lipid peroxidation in both rat liver and brain homogenates to a greater extent than the standard antioxidant, ascorbic acid. F. vulgare may be useful in the management of stress and stress-related disorders on account of its multiple actions such as antistress, memory-enhancing, and antioxidant effects.^[28]

Anticancer activity

Acetone extracts of selected plant species were evaluated for their *in vitro* cytotoxicity against a noncancerous

African green monkey kidney (Vero) cell line and an adenocarcinoma cervical cancer (HeLa) cell line. The plants studied were Origanum vulgare L. (Oregano), Rosmarinus officinalis L. (Upright and ground cove rosemary), Lavandula spica L. (Lavender), Laurus nobilis L. (Bay leaf), Thymus vulgaris L. (thyme), Lavandula x intermedia L. (Margaret Roberts Lavender), Petroselinum crispum Mill. (Curly leaved parsley), Foeniculum vulgare Mill. (Fennel), and Capsicum annuum L. (Paprika). Antioxidant activity was determined using a quantitative DPPH (1,1-diphenyl-2picryl hydrazyl) assay. The rosemary species exhibited adequate radical scavenging capacity with 50% inhibitory concentration (IC₅₀) of μ g/mL and μ g/mL and vitamin C equivalents of 0.351 g 1.09 g for McConnell's Blue and Tuscan Blue, respectively. Cytotoxicity was measured using TXT (Sodium -[1-(phenyl aminocarbonyl)-3,4-tetrazolium]-bis-[4-methoxy-6-nitro] benzene sulfonic acid hydrate) colorimetric assay. Only L. nobilis and O. vulgare exhibited pronounced effects on the HeLa cell line. Dose-dependent studies revealed IC₅₀ of μ g/mL and μ g/mL on the HeLa cells and on the Vero cells 124.1 μ g/mL ± 18.26 and 163.8 μ g/mL ± 2.95 for L. nobilis and O. vulgare, respectively. Light (eosin and hematoxylin staining) and confocal microscopy (Hoechst 33342, acridine orange, and propidium iodide staining) were used to evaluate the cytotoxic mechanism of action for L. nobilis and O. vulgare.^[29]

Antidiabetic activity

Fennel was traditionally reported to be highly recommended for people with diabetes. The essential oil present in *Foeniculum vulgare* possesses an antidiabetic effect in Streptozotocin-Induced diabetic Rats. The results have been reported the marked improvements of hyperglycemia and pathological changes induced by streptozotocin after fennel ingestion, which can prove its effect as antidiabetic in folk medicine.^[35]

Antihepatotoxic activity

Mansour *et al.* $(2011)^{[3\delta]}$ carried out the antihepatotoxic activity using essential oils to prevent liver damage caused by chlorpyrifos (CPH) in rats. Rats poisoning due to exposure to CPF can cause free radicals and an increase in cytochrome P450, resulting in liver dysfunction changes. The antihepatotoxic activity of FEO may be due to its antioxidant activity, the ability to scavenge free radicals generated by CPF, and inhibition of cytochrome P450.

Antithrombotic activity

Fennel essential oil and anethole have been reported to a safe antithrombotic activity,^[37] due to having antiplatelet properties.^[11] *F. vulgare* antithrombotic activity in rats and guinea pig plasma study was carried out. The result showed that the *F. Vulgare* essential oil/anethole had been used as an antithrombotic agent.^[37]

Antioxidant activity

The antioxidant activity of *F. vulgare* as medicine from various Mediterranean countries has been observed. Ahmed *et al.* 2019,^[38] was reported the antioxidant activities of essential oils and ethanol extracts of fennel. Its seeds from Egypt and the Chinese. As a result, The Chinese fennel essential oil showed high activity in DPPH radical scavenging. The Egyptian fennel essential oil showed deficient activity. Pure compounds isolated from fennel showed higher antioxidant activity than the crude extracts.^[10] Essential oils from the azoricum and dulce cultivars were more effective antioxidants than those from the Vulgare cultivar.^[39]

Antifungal activity

The essential oil extracted from *F. vulgare* has been reported to exhibit the antifungal effect. The Fennel essential oil effective as an antifungal agent against *Candida albicans* and *Aspergillus*.^[40] The essential oil of *F. vulgare* has been reported to show a complete zone of inhibition against *Aspergillus niger*, *Aspergillum flavus*, *Fusarium graminearum*, and *Fusarium moniliforme* at six all dose.^[41]

Cardiovascular activity

An aqueous extract of *F. vulgare* leaves possesses potential cardiovascular activities such as reduced blood pressure in rats. Water extract of *F. vulgare* leaves showed a significant dose-related reduction in arterial blood pressure without affecting the heart rate or respiratory rate.^[42]

Anticancer activity

The main content of fennel oil, anethole, shows anticancer activity. Mohamad *et al.* (2011),^[43] studied the anticancer activity of anethole induced in Swiss albino tumor mice. Fennel oil/anethole may reduce oxidative stress and protect mouse cells from damage caused by reactive oxygen species. It could also be used as a safe, effective, and easily accessible source of natural antioxidants.

CONCLUSION

Foeniculum vulgare has emerged as a good source of traditional medicine. It provides a noteworthy basis in pharmaceutical activities to develop/formulate new drugs and future clinical uses. It has considerable importance in particular to the food industry. However, traditional knowledge regarding this plant's use is many but the scientific research available today to support this knowledge is limited. This review article tried to compile information from traditional services and published scientific literature of *Foeniculum vulgare* regarding the medicinal uses. It will be helpful for future researchers to get information.

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