TRADITIONAL AND INTEGRATIVE MEDICINE

Trad Integr Med, Volume 8, Issue 2, Spring 2023

Review

Foeniculum vulgare Mill. from Spice to Pharma: Recent Advances in Its Medicinal Value, Bioactivities and Perspectives

Shilpa Debnath[1], Hardik Kumar[2], Alok Sharma[3]*

[1]*Department of Pharmacognosy, ISF College of Pharmacy, Moga, India*
[2]*Department of Pharmacy Practice, ISF College of Pharmacy, Moga, India*
[3]*Department of Pharmaceutical Technology, MIET, Meerut, India*

Received: 4 Jul 2022 **Revised:** 16 Aug 2022 **Accepted:** 19 Aug 2022

Abstract

Foeniculum vulgare Mill. (*F. vulgare*) belongs to the family Apiaceae with numerous medicinal and traditional applications. It has been widely used in South Asia as an important medicine for the treatment of many ailments. Different parts of *F. vulgare*, including seeds, leaves, aerial part and fruits, has been found to contain diverse phytochemicals, such as anethole, fenchone, limonene, estragole, and p-coumaric acid. In particular, anethole and fenchone as the chief isolated from *F. vulgare*, have been proven to possess notable antioxidant, antitumor, carminative, diuretic, and galactagogue effects and is useful in amenorrhoea, dental decay and irritable bowel syndrome. This review summarizes the botanical activitis, traditional uses, phytochemistry, and pharmacology of *F. vulgare*, along with the clinical studies to serve as the basis for further research and development on this medicinal plant.

Keywords: *Foeniculum vulgare*; Ayurveda; Bioactives; Pharmacology; Clinical study

Introduction

Foeniculum vulgare Mill. is commonly known as "Fennel" in English, "Sounf" in Hindi and "Madhurika" in Sanskrit which belongs to the family Apiaceae (Umbelliferae) [1]. *F. vulgare* commonly differentiated as sweet fennel (*F. vulgare* var. *dulce*) and bitter fennel (*F. vulgare* var. *piperitum*) according to the sub-species and varieties [2]. Fennel is commonly used for various purposes such as culinary, spices, essential oil, vegetable, and medicinal purposes [3]. Entire plant of fennel is used in medicinal industry [4]. Fennel is used medicinally since ancient times, the Greek physicians Hippocrates and Dioscorides declared fennel as a diuretic and its juice was used for treating the eyesight [5], and according to the Indian traditional medicines, fennel is known for its aromatic, stimulant, stomachic, carminative, galactagogue, and emmenagogue properties [6]. Also Chinese people use fennel as carminative, and use it for other purposes such as stomachic, stimulant, relieve chills, abdominal distension, vomiting, and diarrhoea [7].

Due to its medicinal properties fennel is used in different regions according to its medicinal purposes [8]. Hot infusion of fennel is used for improving the lactation, eyesight, open liver and spleen obstructions and treating the amenorrhea; whereas fennel leaves infu-

Citation: Debnath S, Kumar H, Sharma A. ***Foeniculum vulgare* Mill. from Spice to Pharma: Recent Advances in Its Medicinal Value, Bioactivities, and Perspectives**. Trad Integr Med 2023;8(2):217-229.

*Corresponding Author: Alok Sharma
Department of Pharmacognosy, ISF College of Pharmacy, Moga, India
Email: alokalok22@gmail.com

sion used for infants to treat stomach aches in Guyana and Surinam [9]. Fennel fruit aqueous extract is used to relieve flatulent colic in children and infants, and as a diuretic, diaphoretic in India, as well as in Europe. Also, fennel infusion is used for the treatment of flatulence and colic in infants and children [10]. In Europe and Mediterranean countries, fennel is used for various purposes such as an eye wash, antioxidant, analgesic, galactagogue, and snake bites [11]. In Italy, pregnant women are consuming fennel approximately for 3 months [12]. Fennel leaves are used for treating chronic cough, diabetes, mouth ulcer, kidney stones and bronchitis in Southern Italy and Portugal [13]. According to Mexican Traditional Medicine, decoction of fennel can be used for treating tuberculosis, respiratory diseases and as a galactogogue [14]. Palestine people commonly used fennel in their diet and in North East Lebaston, it is used as a digestive [15]. Figure 1 explains the uses of fennel in different regions.

The seeds of *F. vulgare* contain a wide variety of nutrients and other phytochemicals and other parts like leaves also contain several secondary metabolites and possess pharmacological activities [16]. The chemical composition and pharmacology of metabolites discussed in this review provide in accordance that the pharmacology of metabolites confirms the pharmacology of fennel like fenchone, anethole, *p*-coumaric acid, limonene, and estragole possess the activities which are also possessed by fennel like antidiabetic and anticarcinogenic activities. The diverse pharmacological activities of fennel were extensively studied, but only a few were validated. Some of these biological activities include antibacterial activity, antioxidant activity, and anticarcinogenic. Also, clinical studies are performed for dysmenorrhea, menopause symptoms, osteoarthritis, and other diseases which are discussed in this review.

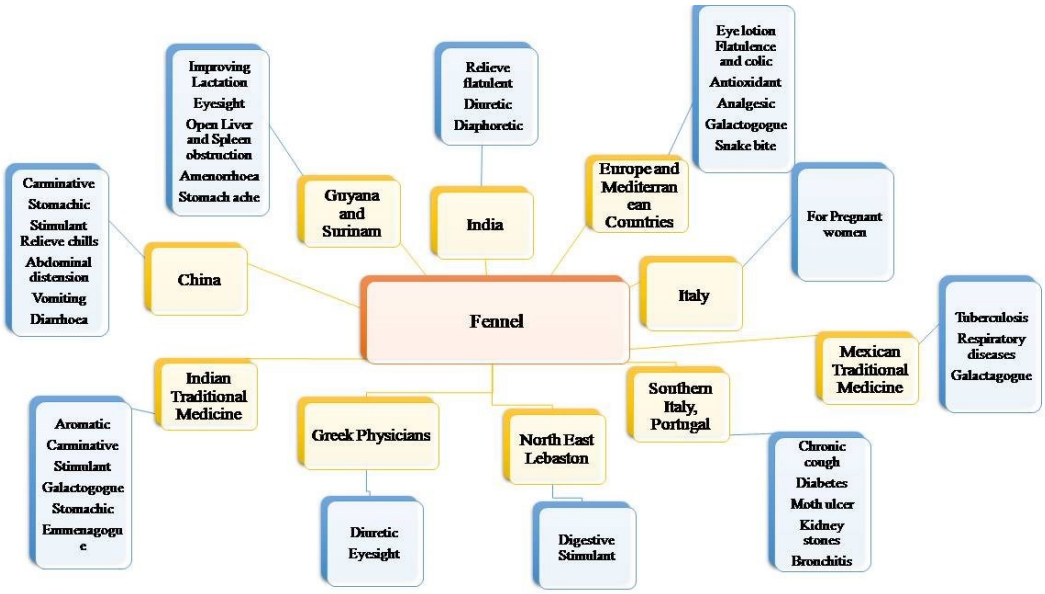

Figure 1. Uses of fennel in different regions

Ayurvedic Uses of Fennel

In Ayurveda, fennel is known as "Shatapushpa", it is sweet in taste and give a cooling effect. Fennel is known for treating digestive disorders and strengthening Agni in Ayurveda. Fennel is useful for calming the nerves; especially its aroma provides mental alertness. Fennel acts on blood, plasma, muscles, nervous system, digestive system, and urinary system. It is known for its stimulant, carminative, diuretic, and antispasmodic properties and is used in the treatment of gas or acidity, indigestion, abdominal cramps or pain, and urinary tract infection (UTI).

As mentioned in Bhavprakash nighantu, (Figure 2) saunf is known by various names in the above-mentioned shloka Chhatra, shatin, shalay, madhura, mishreya, and misi. They are light to digest, piercing, and stimulant; aggravate pitta dosha in the body, hot in potency, and astringent in taste. Saunf is useful in treating disorders like umbilicus-related pain. The herb is useful for other purposes also like stimulat-

शतपुष्पा शताहा च मधुरा कारवी मिसिः। अतिलम्बी सितच्छत्रा संहितच्छत्रिकाऽपि च॥ ८९
छत्रा शालेयशालीनो मिश्रेया मधुरा मिसिः । शतपुष्पा लघुस्तीक्ष्णा पित्तकृद्दीपनी कटुः ॥१०
उष्णा ज्वरानिलश्लेष्मव्रणशूलाक्षिरोगहृत् । मिश्रेया तद्गुणा प्रोक्ता विशेषाद्योनिशूलनुत् ॥११
अग्निमान्द्यहरी हृद्या बद्धविट्कृमिशुक्रहृत् । रूक्षोष्णा पाचनी कासवमिश्लेष्मानिलाहरेत् ॥१२

Figure 2. Shloka from Bhavprakash nighantu

ing the digestive fire, beneficial for treating cardiac problems, constipation, worm infestation, cough, vomiting, and pacifying vata dosha. But excess use of fennel may cause a decrease in sperm quality and quantity.

Taxonomy

Kingdom: Plantae
Division: Tracheophyta
Subdivision: Spermatophytina
Class: Magnoliopsida
Order: Apiales
Family: Apiaceae
Genus: Foeniculum
Species: *vulgare*
Botanical name: *Foeniculum vulgare* Mill.

Botanical Description

Fennel is a seasonal plant with a long history. The fennel plant originated from the southern Mediterranean region, and it now grows wild throughout the Northern, Eastern, and Western hemispheres, notably in Asia, North America, and Europe, thanks to naturalisation and cultivation. It grows wild and is grown in fields. Ancient Egyptians, Romans, Indians, and Chinese were all familiar with the plant. It was grown by the Romans for its fragrant seeds, and the delicious fleshy shoots are still a popular food in southern Italy [17]. It is said that Emperor Charlemagne encouraged its development in Central Europe. In current French and Italian cookery, it is a must-have ingredient. The plant's entire body is aromatic and may be used in a variety of ways. *F. vulgare* is a perennial plant with delicate, feathery, almost hair-like leaf that grows up to 6.6 feet (2 m) tall [18]. This plant has a dill-like appearance. Its anise-flavoured leaf and seeds, both of which are often gathered for use in cooking, are commonly planted in vegetable and herb gardens [19]. It is upright and cylindrical, brilliant green and smooth, with several branching leaves split into the tiniest of segments [20]. The leaves may grow up to 40 cm long and are finely divided, having filiform (threadlike) final segments that are around 0.5 mm broad. In July and August, the bright golden blooms with thirteen to twenty rays bloom in big, flat terminal umbels [21].

Chemical Composition

Hina *et al*. reported, protein content (9.38±0.39) in fennel seed sample was evaluated using Kjeltech Apparatus, and fat content (9.76±0.34) in fennel seed was determined using hexane as solvent in Soxtec System fibre during the composition profiling of Fennel seeds. Flame Photometer-410 was used to estimate sodium, potassium, and calcium, while an Atomic Absorption Spectrophotometer was utilised to evaluate zinc, iron, manganese, and other minerals in the digested HNO3 sample of fennel seeds. A significant amount of minerals, including potassium (852.45±33.25 mg/100 g), calcium (580.6±24.39 mg/100 g), manganese (211.35±7.40) mg/100 g, sodium (16.21±0.65 mg/100 g), and iron (9.72±0.38 mg/100 g), but zinc was only identified in trace amounts [22,23]. Diao et al., (2014) used gas chromatography-mass spectrometry (GC-MS) to examine the chemical components of the essential oil derived by hydrodistillation of fennel seeds, and 28 components were discovered. The primary components were determined to be trans-anethole (68.53%) and estragole (10.42%). Trans-anethole (59.8–90.4%) was the main constituent of the essential oils of fresh leaves [24]. In another study, the principal components recovered by microwave hydrodistillation from fennel seeds essential oil were (E)-anethole (79.0 %-81.6 %), fenchone (8.7% -10.9 %), estragole (4.0 %- 4.2 %), and limonene (3.2%-3.5%). More than 97% of the total essential oil is made up of these four components [25]. In another study, essential oils of the seed of three organically grown cultivars of fennel were compared which demonstrated the presence of eighteen main monoterpenoids. However, there were considerable variances in the percentages of the components. All of the oils studied had high levels of trans-anethole (5%-61 %), estragole (57 %), fenchone (7%-13 %), and limonene (12%-28 %) [26]. According to Pavela et al., (2016) the majority of trans-anethole (48.42–63.23%) was found in fennel essential oils when they compared the aerial section and seeds of fennel. The essential oils derived from seeds contained the most

trans-anethole (60%) [27,28]. In another study, Olgun et al., (2017) used a screw press to extract the oil from fennel seeds, and the oil contained the most prevalent component, anethole (89.74%) [29]. Coban et al., (2018) reported the major compound in fennel fruit oil was anethole (90.71–91.62%), followed by estragole (3.60–4.02%), limonene (2.19–3.24%), and fenchone (0.96–1.55%) [30].

Alam et al., (2019) reported about the methanolic extract of *F. vulgare* using the GC–MS method, fifty-seven distinct phytoconstituents were discovered where trans-anethole (31.49%), 2-pentanone (25.01%), fenchone (11.68%), and benzaldehyde-4-methoxy were the most common compounds found (8.01%) [31]. Kalleli et al., (2019) compared essential oil and extract of two cultivars and reported primary components which are trans-anethole and estragole ranging (63.41% –78.26%) and (44.72% –88.92%), respectively. All fennel seed extracts had a high content of quinic acid, 4-O-caffeoylquinic acid, *p*-coumaric acid, and 4-Ocaffeoylquinic acid, which defined their phenolic composition [32]. According to Abdellaoui et al., (2020) when they compared wild fennel and cultivated fennel, the wild fennel essential oil has the highest phenolic concentration (222.24 mg/mL). The primary compounds found in both wild and cultivated fennel were estragole, anethole, and fenchone, according to chromatography analyses. Cultivated fennel, on the other hand, has a higher concentration of estragole and a lower concentration of anethole than wild fennel. The chemical profiles of the other compounds were nearly identical, with slight quantitative differences [33]. Chemical composition is explained in table 1.

Pharmacology of metabolites of *F. vulgare*

F. vulgare is enriched with several bioactive compounds. Among these anethole, limonene, fenchone, estragole and *p*-coumaric acid were examined for pharmacological activities (Table 2). Formulations based on this medicinal plant were used in Ayurveda, Chinese Traditional Medicine and Mexican Traditional Medicine. Anethole, limonene, *p*-coumaric acid and estragole are known for their anti-inflammatory effect, which can help against diseases like cancer, neurodegeneration and wound healing. It is believed that introduction of hydroxyl groups at double bond from propenyl moiety of anethole enhances the anti-inflammatory activity. Anethole, limonene, and *p*-coumaric acid are known for its anticancer activity; while both anethole and limonene possess antidiabetic activity.

Pharmacological activity of Fennel

Antibacterial Activity

According to the Diao et al., (2014), results of MIC and MBC, Gram positive and Gram negative bacteria strains had different sensitivities to the essential oil of fennel seeds, and the essential oil exhibited antibacterial activity against *Staphylococcus albus, Bacillus subtilis, Salmonella typhimurium, Shigella dysenteriae,* and *Escherichia coli. S. dysenteriae* was the most sensitive to essential oil amongst the bacteria tested, with MIC value of 0.125 and MBC value of 0.25 mg/mL [23]. In another study, Kwiatkowski et al., (2019) reported antibacterial activity of fennel essential oil against 76.7% of isolates at the concentrations of 2.0% and 2.5% [58]. Marín et al., (2016) reported that, when more than 40 µL fennel essential oil was present in the discs, inhibition zone of 10 mm demonstrated antibacterial activity against L. innocua [59]. Shabnam et al. reported fennel oil was found to be fairly potent against bacterial strains, possessing the antibacterial activity against Gram positive bacterium Bacillus subtilis (3.8 cm zone of inhibition) [60].

Antioxidant Activity

Many aromatic and medicinal plants possess antioxidant effects which have been demonstrated to be beneficial in slowing the process of lipid peroxidation in oils and fatty diets, therefore demands for these plants are increased. Extracts of *F. vulgare* showed potent free radical scavenging activity in 2,2-Diphenyl-1-picrylhydrazyl (DPPH) antioxidant text. Methanol and ethanol extracts had higher free radical scavenging activity than other solvents. Furthermore, methanol extracts outperformed ethanol extracts in terms of scavenging efficacy [61]. Essential oil of fresh leaves of *F. vulgare* was found to show weak capacity ranging from 0.25 to 0.33 mmol/L due to their anethole level [24]. Essential oil of fennel seeds found to show maximum activity (0.35-0.04) in quenching the DPPH radical [26]. In another study, both extracts and essential oils of fennel seeds, ethanol extracts of seeds have a high capacity to scavenge DPPH radicals [62]. Similarly, in another study, it is reported that methanolic fennel seed extracts in general have a stronger ability to scavenge DPPH radicals than fennel essential oils and therefore, methanolic extract (IC_{50} = 27.17 g/mL) demonstrated the strongest antioxidant properties [32]. Hydroalcoholic extracts of fennel leaves, showed the Relative Antioxidant Capacity Index (RACI) value (0.844) for antioxidant activity [63]. It can be assumed that variation of antioxidant activity may be caused due to the trans-anethole content in fennel.

Anti-Carcinogenic Activity

Various studies have been conducted which show the anticancer activity of fennel. In one such study fennel seed methanolic extract (FSME) was found to possess significant cytoprotective effect against gamma irradiation, as evidenced by the restoration of MDA

Table 1. Chemical constituents of Foeniculum vulgare

S. No.	Plant Parts used	Extraction techniques	Sample used	Analysis Techniques	Total Components	Major Components	Ref.
1.	Fennel seeds	Hydrodistillation	Essential oil	GC/MS	28 components	Trans-anethole (68.53%) Estragole (10.42%)	34
2.	Fresh leaves	Hydrodistillation	Essential oil	GC/MS and GC	60 compounds	Trans-anethole (59.8%-90.4%)	24
3.	Fennel seeds	Microwave Hydrodistillation	Essential oil	GC/MS and GC analysis	17 volatile compounds	E-anethole (79.0%) Fenchone (10.9%) Estragole (4.2%) Limonene (3.2%)	35
4.	Fennel seeds	Hydrodistillation	Essential oil	GC/MS analysis	18 monoterpenoids	Trans-anethole (5%-61%) Estragole (57%) Fenchone (7%-!3%) Limonene (12%-28%)	26
5.	a) Aerial section of plants	Hydrodistillation	Essential oil	GC/MS analysis	7-14 compounds	Trans-anethole (48.42%-63.23%)	27
	b) Seeds	Hydrodistillation	Essential oil	GC/MS analysis	7-14 compounds	Trans-anethole (60%)	
6.	Seeds	Screw-press	Essential oil	GC/MS	-	Anethole (89.74%) D-limonene (3.41%)	29
7.	Fruit	Hydrodistillation	Essential oil	GC/MS, GC/FID	-	Anethole (90.71%-91.62% Estragole (3.60%-4.02%) Limonene (2.19%-3.24%) Fenchone(0.96%-1.55%)	36
8.	Seed	Soxhlet Extraction	Methanolic Extract	GC/MS	57 components	Trans-anethole (31.49%) 2-pentanone (25.01%) Fenchone (11.68%) Benzaldehyde-4-methoxy (8.01%)	31
9.	Seeds	Hydrodistillation	Essential oil	GC/MS	24 compounds	Trans-anethole (74.8%-78.2%) Estragole (88.92%) L-Fenchone (10.64%-12.09% Limonene (5.65%-6.32%)	37
	Seeds	-	Extract	LC/MS	33 compounds	Quinic acid (4.6% to 5.023%) 4-O-caffeoylquinic acid (3.12% to 6.36%) p-coumaric acid (2.7 to 4.2%)	
10.	Seed	Steam Distillation	Essential oil	GC/MS	21 compounds	Estragole (60.01%-35.33%) Anethole (22.15%-52.27%) Fenchone (6.50%-4.32%)	33

levels, catalase activity, and GSH content to near-normal levels before irradiation. This show to be effective against a breast cancer cell line (MCF7) as well as a liver cancer cell line (HepG-2). In Ehrlich ascites carcinoma (EAC)-bearing mice with or without radiation exposure, FSME had an anticancer impact through regulating lipid peroxidation and enhancing the antioxidant defence system [64]. Similarly in another study, ethanolic extracts of fennel cause apoptosis and limit cell proliferation in vitro, with fennel hav-

Table 2. Pharmacology of metabolites of *F. vulgare*

Chemical Components	Pharmacological/ Therapeutic effect	References
Anethole	Antidiabetic activity	38
	Neuroprotective	39
	Anti-cancer activity	40
	Anti-oxidant Activity	41
	Anti-cataract activity	42
	Gastro protector activity	41
	Local anaesthetic activity	43
Limonene	Antioxidant activity	44
	Anti-cancer activity	45
	Anti-nociceptive activity	46
	Antidiabetic ativity	47
	Anti-inflammatory activity	48
Fenchone	Antidiarrheal activity	49
	Antinociceptive Activity	50
	Cytotoxicity	51
	Anti-inflammatory activity	52
	Anti- microbial activity	53
Estragole	Antioxidant	54
	Antimicrobial	55
	Anxiolytic	56
p-coumaric acid	Anti-oxidant activity	57

ing the most antiproliferative impact. Breast cancer in mice the 4T1 cell line was treated with various extract dosages. The Bromo-2′-deoxyuridin test was used to measure cell proliferation after 24 h, and the dose of 50 g/mL of fennel had the best inhibitory effect [64]. A methanolic extract of *F. vulgare* causes DNA damage in cancer cell lines, frequently in MCF-7 cell lines than in HEPG-2 and HCT 116 cell lines. Also it has the ability to activate p53 gene expression in cancer cell lines. Because of their broad-spectrum antiplatelet activity and vasorelaxant action, the essential oil of *F. vulgare* and its primary component, anethole, has been proven to have a safe antithrombotic effect. As a result, fennel may have anticancer properties [65]. In another study, the anticancer potential of seed oil in vitro against human breast cancer (MDA-Mb) and cervical epithelioid carcinoma (Hela) cell lines by MTT assay found to be a very effective anticancer agent in both cases, with an IC50 of less than 10 g/mL in both cases [34]. In another study, the oil mixture (fennel oils and geranium oils) induced selective cytotoxicity in MCF-7 cells by inducing cell cycle arrest and death, which could be produced by the synergistic action. Also, the fennel and clove oil mixture caused selective cytotoxicity in Caco-2 cells, including cell cycle arrest and apoptosis, which could be due to synergistic effects [66]. Ghasemian et al., (2020) reported that, on the MCF-7 cancer cell line, fennel oil extracted from three different locations had higher cytotoxic effects. Anticarcinogenic activity is explained in table 3.

Anti-inflammatory Properties

Oral treatment of a methanol extract of *F. vulgare* fruit to rats and mice inhibited acute and subacute inflammatory disorders in both rats and mice. Three screening methods were used to assess the anti-inflammatory effect of methanol extract: carrageenan-induced paw edema, arachidonic acid-induced ear edema, and formaldehyde-induced arthritis. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly tested with these. In the case of acute inflammation, methanol extract (200 mg/kg) inhibits paw edema generated by carrageenan injection by 69% as compared to the control group of mice. In mice, a methanol extract of *F. vulgare* reduces arachidonic acid-induced ear edema by 70%. In the presence of methanolic extract of *F. vulgare* on inflammation produced by formaldehyde, serum transaminase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels considerably increased as compared to the control group. The measurement of AST and ALT levels is a useful and easy way to determine the anti-inflammatory activity of the target substances [69]. *F vulgare* FME may affect both the cyclooxygenase and lipoxygenase pathways, according to these findings [70].

Expectorant Activity

The ciliary motility of the respiratory apparatus is stimulated by *F. vulgare* seeds, which improves the external transport of extraneous corpuscles. This effect implies that fennel might be used to treat bronchi-

Table 3. Anticarcinogenic activity of *F. vulgare*

S. No.	Parts of plant used	Type of extract	Activity	Effective against	References
1.	Seeds	Methanolic extract	Cytoprotective	Breast cancer cell , Liver cancer cell line	64
2.	Seeds	Ethanolic extract	Antiproliferative	Breast cancer	64
3.	Seeds	Methanolic extract	Damage in cancer cell lines	Damage cancer cell line	65
4.	Seeds	Essential oil	Anti-cancer	Breast cancer, Cervical epitheloid, Carcinoma cell lines	67
5.	Seeds	Essential oil	Cytotoxicity	CaCO2 cells, Apoptosis	66
6.	Seeds	Essential oil	Cytotoxicity	MCF-7 cancer cell lines	68

al and bronchopulmonary diseases, as well as in polluted surroundings [69]. The volatile oil of *F. vulgare* causes the smooth muscles of the trachea to contract, which may help with the expectoration of mucus, germs, and other corpuscles that are not native to the respiratory tracts [71].

Anticolitic Activity

Fennel essential oil reduces intestinal gas; while also regulating the movement of smooth muscles in the gut. *F. vulgare* is used to treat spastic gastrointestinal disturbances, certain kinds of chronic colitis (that do not respond to conventional therapies), dyspepsia from gastrointestinal atony, and dyspepsia with a feeling of heaviness in the stomach. The inclusion of fennel to laxatives containing anthraquinones lowers the occurrence of stomach discomfort [72].

Antinocioceptive Activity

Antinociceptive refers to any substance that suppresses nociception, the physiological mechanism that causes pain. Hexane, methylene chloride, ethyl acetate, and methanolic extract from the aerial part of *F. vulgare* demonstrated considerable antinociceptive action against acetic acid-induced writhing in mice. The antinociceptive activity of the methanolic extract of *F. vulgare* aerial parts was highest at a dosage level of 2000 mg/kg; whereas the activity of the ethyl acetate extract was highest at a dose level of 800 mg/kg. On the other hand, n-hexane extract (700 mg/kg) and methylene chloride extract (500 mg/kg) displayed antinociceptive activity that was comparable to that of the peripheral antinociceptive reference medication (acetyl salicylic acid) [73].

Diuretic Activity

Any chemical that encourages the production of urine is referred to as a diuretic. It's a diuretic that promotes diuresis in a nutshell. Diuretics diminish the amount of blood flowing through the cardiovascular system by encouraging the evacuation of urine (measured as urine volume [UV] discharged) and urinary sodium (UNa) from the body. Caceres et al. conducted a trial in which they gave a powdered extract of the complete plant (*F. vulgare*) to conscious animals and found that it had no impact on UV or UNa. The ethanolic extract of the fruit of *F. vulgare* showed outstanding diuretic action, proving the older folk claim of *F. vulgare*, which was recorded in the United States of America. The fruit extract had a diuretic effect that was statistically significant [74]. In mice with a urine production nearly double that of the control group, *F. vulgare* produced diuresis (500mg/kg dosage) was equivalent to that of the reference diuretic drug urea (960mg/kg dose). Changes in sodium and/or potassium excretion were not linked to diuresis [75]. The authors also found that *F. vulgare* had no influence on the noradrenalin contractile responses of aortic rings in another phase of the investigation, suggesting that it acted primarily as a diuretic and natriuretic with little effect on arterial vascular tone [76].

Cardiovascular Activity

Aqueous extracts of *F. vulgare* leaves have been shown to have possible cardiovascular effects. Pentobarbital-anaesthetized male albino Sprague-Dawley rats were used to test this effect. The lyophilized boiling water extract of leaves exhibited a substantial dose-related drop in arterial blood pressure without changing heart rate or respiration rate when given intravenously. The nonboiled aqueous extract, on the other hand, has virtually little hypotensive action. The hypotensive impact of the boiling water extract did not appear to be mediated by adrenergic, muscarinic, ganglionic, or serotonergic receptors, although histamine antagonists did block the hypotensive effect in a

dose-dependent manner [77].

Oculohypotensive Activity

Using a water loading and steroid induced glaucoma paradigm, the aqueous seed extract of *F. vulgare* showed considerable oculohypotensive action. At 0.3 %, 0.6 %, and 1.2 % (w/v) concentrations, this extract reduced intraocular pressure by 17.49, 21.16, and 22.03 % in normotensive rabbits, respectively. In a water loading experimental animal model, a maximum mean difference of 31.20 % was detected between vehicles treated and extracts treated eyes, while a maximum mean intraocular pressure decrease of 31.29 % was recorded in a steroid induced glaucoma model. Thus, the aqueous extract of *F. vulgare* showed oculohypotensive action that was comparable to that of timolol, a reference standard antiglaucoma medication [78].

Estrogenic Activity

For centuries, *F. vulgare* has been utilised as an estrogenic substance. It has been said to boost libido, encourage menstruation, ease labour, lessen the effects of the male climacteric, and improve milk supply. In a study, it was shown that the extract of fennel increased serum concentrations of follicle-stimulating hormone and decreased the yolk hormones and testosterone in treatment groups [79]. In another study Devi et al. investigated fennel fruit acetone extract effect on mammary gland and oviduct. The outcomes of this investigation supported this plant seed extract's effects on natural oestrogen [80]. Anethole, the primary component of fennel essential oil, is thought to be the active oestrogenic substance. Anethole polymers like diantethole and photoanethole may really be the pharmacologically active substances, according to several other investigations [81].

Hepatoprotective Activity

There have been reports that the fennel essential oil possesses hepatoprotective properties. Fennel essential oil was reported to reduce the hepatotoxicity caused by acute CCl4 injection in a research, with evidence of lower levels of blood AST, ALT, alkaline phosphatase (ALP), and bilirubin [82]. In another study, fennel oil has shown a significant hepatoprotective effect against CCL4-induced liver damage in rats. Therefore, people who suffer from liver illnesses linked to oxidative stress may benefit from the use of fennel oil in dietary formulations [83].

Antidiabetic Activity

A research study showed aqueous extracts from fennel, affected blood sugar levels and had anti-diabetic effects. The results showed that the extract might be helpful for diabetic patients to regulate blood glucose, and that regular usage could be successful in lowering chronic problems related to diabetes [84]. To evaluate the effect of fennel on blood sugar reduction, a study was conducted on streptozotocin-diabetic rats. According to the results, fennel extract reduces hyperglycemia in diabetic rats, which is partly due to the herb's impact on the oxidation/restored system. Consequently, this plant can be utilised in the pharmaceutical industry to create anti-diabetic drugs [85].

Memory-Protective Activity

Fennel herbs are said to be used to improve memory and intelligence. So, it was investigated how fennel extract affected memory in amnesic rats. The findings indicated that this extract has the ability to improve memory [20]. In a research by Joshi et al., the anti-acetylcholinesterase and neurotropic effects of fennel extract on mice were examined. The results of this investigation demonstrated a substantial inhibition of acetylcholinesterase by fennel extract. This study suggests that fennel may be useful in the treatment of cognitive illnesses including dementia and Alzheimer's [86].

Clinical Studies

Dysmenorrhea

Omidvar et al., (2012) investigated to see if *F. vulgare* had a clinical effect on primary dysmenorrhoea. The study group received a 30 mg fennel extract capsule from the start of their menstrual period, whereas the placebo group received a capsule containing wheat flour in the same dose. A 10-point linear analogue approach was used to assess pain intensity. In terms of pain alleviation, the study group outperformed the placebo group (P:0.05). According to the findings, fennel is an efficient herbal treatment for menstruation pain [87]. The effects of oral fennel drop for treating primary dysmenorrhea were studied by Bokaie et al., (2013) [88]. Fennel appears to be helpful in lowering the severity of dysmenorrhea.

Menopause

Archer et al., (2017) study reported that fennel may help postmenopausal women manage their menopausal symptoms. Ninety postmenopausal women were randomly allocated to treatment or placebo groups in this triple-blind, placebo-controlled experiment. The subjects were given either 100 mg fennel soft capsules or a placebo. Before the intervention, the groups had equal mean scores on the Menopause Rating Scale (MRS) questionnaire. The treatment group's mean MRS score decreased significantly after intervention. The findings suggested that fennel is a safe and effective medication for reducing menopausal symptoms in postmenopausal women [89]. Mahdavian et al., (2019)

performed trial is to see if combined herbal remedies including a specified amount of fennel can help with menopause symptoms and the results suggested that physical, psychological, and urogenital categories all improved significantly after a 12-week extracts treatment [90].

Overweight

In another study, Bae et al., (2015) investigated using drinking tea made from the medicinal herb fennel affected overweight Korean women's perceived hunger. In comparison to the PT, Fennel Tea consumption resulted in lower hunger, less prospective food consumption, and increased sensations of fullness (p 0.05). Fennel Tea was found to be a highly effective assistance in suppressing subjective appetite in overweight women in South Korea [91].

Idiopathic Hirsutism

Akha et al., (2014) performed trial to see if fennel topical gel may help with mild to moderate idiopathic hirsutism. After 24 weeks, the hair thickness of patients who received fennel gel decreased from 97.931.5 to 75.626.7 micron (P0.001). Results suggested that fennel gel at 3% is beneficial in reducing hair thickness in women with idiopathic mild to moderate hirsutism [92].

Dental Decay

Saliva is an oral fluid that acts as a barrier against dental decay. The Indian Subcontinent has a tradition of chewing fennel seeds after meals. The Manohar et al., (2020) wanted to measure the baseline pH of saliva as well as the changes in salivary pH after eating fennel seeds and results suggested that fennel seeds,

Figure 3. Clinical studies of fennel formulation of various disorders

when chewed, raise the pH of saliva, making it an effective anticariogenic agent [93].

Irritable Bowel Syndrome

The efficacy of bio-optimized turmeric and essential fennel oil extracts in irritable bowel syndrome (IBS) patients was investigated by [94] in an open pilot trial. The results of this "real-life" study show that the combination of curcumin and fennel essential oil may be a useful therapeutic approach in IBS patients, owing to its beneficial effects on both symptoms and quality of life (QoL), at least for the time period observed.

Osteoarthritis

Alazadeh et al., (2020) investigated to explore if the seed extract of *F. vulgare* could help women with knee osteoarthritis. The fennel group had a higher percentage change than the placebo group as well as the impact magnitude was larger in the fennel group than in the placebo group, especially in the pain variable based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire and Visual Analog Scale (VAS). The findings suggested that fennel could be a good supplemental treatment option for patients with knee osteoarthritis [95]. Figure 3 explains the clinical studies of fennel formulation of various disorders.

Conclusion

Fennel is well known for its traditional uses like carminative, diuretic, amenorrhoea, and galactogogue. Even according to ayurveda it is believed to aggravates pitta dosha in the body and also pacify vata dosha. The main components are analysed in fennel are trans-anethole, limonene, fenchone, *p*-coumaric acid and estragole and some of them exhibits pharmacolog-

ical activities like anti-inflammatory, anti-cancer and anti-diabetic activity. Pharmacology of metabolites explains that fennel can be more beneficial, then it is discussed till now in the experiments. In this review, pharmacological activity of fennel is also discussed although more pharmacological activity of fennel can be tested according to its traditional uses and pharmacology of its metabolites. Clinical studies confirm the activity of fennel to treat the dysmenorrhoea, menopause, dental decay and irritable bowel syndrome. In conclusion, various studies are conducted on fennel and more research studies can be done to explore the medicinal uses fennel. It could be incorporated in a successful formulation having define markers and productive medicinal uses.

Conflict of Interests

The authors declare no competing interests.

Acknowledgements

We gratefully thank the department of pharmacognosy for their valuable suggestion and assistance.

References

[1] Naquibuddin M, Hamiduddin, Reyaz Z. Badiyan (Foeniculum Vulgare Mill .): an important drug of Unani Badiyan (Foeniculum Vulgare Mill.): an important drug of unani system of medicine. Eur J Pharm Med Res 2020;7:307-312.

[2] Malhotra SK. Recent advances in seed spices research–a review. Ann Plant Soil Res 2016;18:300-308.

[3] Roby MHH, Sarhan MA, Selim KAH, Khalel KI. Antioxidant and antimicrobial activities of essential oil and extracts of fennel (Foeniculum vulgare L.) and chamomile (Matricaria chamomilla L.). Ind Crops Prod 2013;44:437-445.

[4] Rather MA, Dar BA, Sofi SN, Bhat BA, Qurishi MA. Foeniculum vulgare: A comprehensive review of its traditional use, phytochemistry, pharmacology, and safety. Arab J Chem 2016;9:S1574-S1583. doi:https://doi.org/10.1016/j.arabjc.2012.04.011

[5] Ody P. The Complete Medicinal Herbal: A Practical Guide to the Healing Properties of Herbs. Simon and Schuster 2017.

[6] Akbar S. Fennel (Foeniculum vulgare Mill .): A Common spice with unique medicinal properties. Ann Complement Altern Med 2018;1:1-12.

[7] Keys JD. Chinese herbs, Their Botany, Chemistry, and Pharmacodynamics, Charles E. Tuttle Company, Inc Rutland, Vermont Tokyo, Japan 1976.

[8] Saddiqi H, Iqbal Z. Usage and significance of fennel (Foeniculum vulgare Mill.) seeds in eastern medicine. Nuts Seeds Heal Dis Prev 2011:461-467

[9] Bekoe EO, Kitcher C, Gyima NAM, Schwinger G, Frempong M. Medicinal plants used as galactagogues. Pharmacogn Plants 2018.

[10] Colombo ML. Herbal preparations and homemade herbal teas for children: The matter of fennel. Nutrafoods 2012;11:19-24.

[11] Gori L, Gallo E, Mascherini V, Mugelli A, Vannacci A, et al. Can estragole in fennel seed decoctions really be considered a danger for human health? a fennel safety update. Evid Based Complement Alternat Med 2012;2012:860542.

[12] Facchinetti F, Pedrielli G, Benoni G. Herbal supplements in pregnancy: unexpected results from a multicentre study. Hum Reprod 2012;27:3161-3167.

[13] Al-Snafi AE. Traditional uses of Iraqi medicinal plants (part 2). Int J Biol Pharm Sci Arch 2021;2:022-041.

[14] McGaw LJ, Omokhua-Uyi AG, Finnie JF, Van Staden J. Invasive alien plants and weeds in South Africa: A review of their applications in traditional medicine and potential pharmaceutical properties. J Ethnopharmacol 2022;283:114564. doi:https://doi.org/10.1016/j.jep.2021.114564

[15] Jeambey Z, Johns T, Talhouk S, Batal M. Perceived health and medicinal properties of six species of wild edible plants in north-east lebanon. Public Health Nutr 2009;12:1902-1911.

[16] Makkar HPS, Norvsambuu T, Lkhagvatseren S, Becker K. Plant secondary metabolites in some medicinal plants of mongolia used for enhancing animal health and production. Vet Res 2009:159-167.

[17] Krishnamurthy KH. Medicinal plants: Madhurika, saunf or fennel (Foeniculum vulgare, Gaertn). J New Approaches to Med Heal 2011;19:1-4.

[18] Gani HMO, Hoq MO, Tamanna T. Pharmacological and phytochemical analysis of Foeniculum vulgare Mill: A review. 2019;198272954

[19] Malhotra SK. Fennel and fennel seed. In: Handbook of Herbs and Spices. Elsevier; 2012:275-302.

[20] Badgujar SB, Patel VV, Bandivdekar AH. Foeniculum vulgare Mill: a review of its botany, phytochemistry, pharmacology, contemporary application, and toxicology. Biomed Res Int 2014;842674.

[21] Ara RIT. Ph ton eBooks. Published online 2015.

[22] Bukhari H, Shehzad A, Saeed K. Compositional profiling of fennel seed. Pakistan J Food Sci. 2014;24:132-136.

[23] Diao WR, Hu QP, Zhang H, Xu JG. Chemical composition, antibacterial activity and mechanism of action of essential oil from seeds of fennel (Foeniculum vulgare Mill.). Food Control 2014;35:109-116.

[24] Senatore F, Oliviero F, Scandolera E, Taglialatela-Scafati O, Roscigno G, et al. Chemical composition, antimicrobial and antioxidant activities of anethole-rich oil from leaves of selected varieties of fennel [Foeniculum vulgare Mill. ssp. vulgare var. azoricum (Mill.) Thell]. Fitoterapia 2013;90:214-219.

[25] González-Rivera J, Duce C, Falconieri D, Ferrari C, Ghezzi L, et al. Coaxial microwave assisted hydrodistillation of essential oils from five different herbs (lavender, rosemary, sage, fennel seeds and clove buds): Chemical composition and thermal analysis. Innov Food Sci Emerg Technol 2016;33:308-318.

[26] Chang S, Mohammadi Nafchi A, Karim AA. Chemical composition, antioxidant activity and antimicrobial properties of three selected varieties of Iranian fennel seeds. J Essent Oil Res 2016;28:357-363.

[27] Pavela R, Žabka M, Bednář J, Tříska J, Vrchotová N. New knowledge for yield, composition and insecticidal activity of

essential oils obtained from the aerial parts or seeds of fennel (Foeniculum vulgare Mill.). Ind Crops Prod 2016;83:275-282.

[28] Nagoor Meeran MF, Javed H, Taee H Al, Azimullah S, Ojha SK. Pharmacological properties and molecular mechanisms of thymol: Prospects for its therapeutic potential and pharmaceutical development. Front Pharmacol 2017;8:1-34.

[29] Olgun Ç, Özkan OE, Güney B, Pattabanoglu ES, Güney K, et al. Chemical composition and antimicrobial activity in cold press oil of fennel, anise, white and black mustard seeds. Indian J Pharm Educ Res 2017;51:S200-S204.

[30] Coban F, Ozer H, Ors S, Sahin U, Yildiz G, et al. Effects of deficit irrigation on essential oil composition and yield of fennel (Foeniculum vulgare Mill) in a high-altitude environment. J Essent Oil Res 2018;30:457-463.

[31] Alam P, Abdel-Kader MS, Alqarni MH, Zaatout HH, Ahamad SR, et al. Chemical composition of fennel seed extract and determination of fenchone in commercial formulations by GC-MS method. J Food Sci Technol 2019;56:2395-2403.

[32] Kalleli F, Bettaieb Rebey I, Wannes WA, Boughalleb F, Hammami M, et al. Chemical composition and antioxidant potential of essential oil and methanol extract from Tunisian and French fennel (Foeniculum vulgare Mill.) seeds. J Food Biochem 2019;43:e12935

[33] Abdellaoui M, Bouhlali E dine T, Derouich M, El-Rhaffari L. Essential oil and chemical composition of wild and cultivated fennel (Foeniculum vulgare Mill.): A comparative study. South African J Bot 2020;135:93-100.

[34] Akhbari M, Kord R, Jafari Nodooshan S, Hamedi S. Analysis and evaluation of the antimicrobial and anticancer activities of the essential oil isolated from Foeniculum vulgare from Hamedan, Iran. Nat Prod Res 2019;33:1629-1632. doi:10.1080/14786419.2017.1423310

[35] González-Rivera J, Duce C, Falconieri D, Ferrari C, Ghezzi L, et al. Coaxial microwave assisted hydrodistillation of essential oils from five different herbs (lavender, rosemary, sage, fennel seeds and clove buds): Chemical composition and thermal analysis. Innov Food Sci Emerg Technol 2016;33:308-318.

[36] Coban F, Ozer H, Ors S, Sahin U, Yildiz G, et al. Effects of deficit irrigation on essential oil composition and yield of fennel (Foeniculum vulgare Mill) in a high-altitude environment. J Essent Oil Res 2018;30:457-463.

[37] Kalleli F, Bettaieb Rebey I, Wannes WA, Boughalleb F, Hammami M, et al. Chemical composition and antioxidant potential of essential oil and methanol extract from Tunisian and French fennel (Foeniculum vulgare Mill.) seeds. J Food Biochem 2019;43:e12935.

[38] Sheikh BA, Pari L, Rathinam A, Chandramohan R. Trans-anethole, a terpenoid ameliorates hyperglycemia by regulating key enzymes of carbohydrate metabolism in streptozotocin induced diabetic rats. Biochimie 2015;112:57-65.

[39] Wang B, Zhang G, Yang M, Liu N, Li Y-X, et al. Neuroprotective effect of anethole against neuropathic pain induced by chronic constriction injury of the sciatic nerve in mice. Neurochem Res 2018;43:2404-2422.

[40] Elkady AI. Anethole inhibits the proliferation of human prostate cancer cells via induction of cell cycle arrest and apoptosis. Anticancer Agents Med Chem 2018;18:216-236.

[41] Freire RS, Morais SM, Catunda-Junior FEA, Pinheiro DCSN. Synthesis and antioxidant, anti-inflammatory and gastroprotector activities of anethole and related compounds. Bioorg Med Chem 2005;13:4353-4358.

[42] Dongare V, Kulkarni C, Kondawar M, Magdum C, Haldavnekar V, et al. Inhibition of aldose reductase and anti-cataract action of trans-anethole isolated from Foeniculum vulgare Mill. fruits. Food Chem 2012;132:385-390. doi:10.1016/j.foodchem.2011.11.005

[43] Moradi J, Abbasipour F, Zaringhalam J, Maleki B, Ziaee N, et al. Anethole, a medicinal plant compound, decreases the production of pro-inflammatory TNF-α and IL-1β in a rat model of LPS-Induced Periodontitis. Iran J Pharm Res 2014;13:1319-1325.

[44] Roberto D, Micucci P, Sebastian T, Graciela F, Anesini C. Antioxidant activity of limonene on normal murine lymphocytes: relation to H2O2 modulation and cell proliferation. Basic Clin Pharmacol Toxicol 2010;106:38-44.

[45] Yu X, Lin H, Wang Y, Lv W, Zhang S, et al. d-limonene exhibits antitumor activity by inducing autophagy and apoptosis in lung cancer. Onco Targets Ther 2018;11:1833-1847.

[46] Hilário S, Amaral IA, Gonçalves MFM, Lopes A, Santos L, et al. Diaporthe species associated with twig blight and dieback of Vaccinium corymbosum in Portugal, with description of four new species. Mycologia 2020;112:293-308.

[47] Murali R, Saravanan R. Antidiabetic effect of d-limonene, a monoterpene in streptozotocin-induced diabetic rats. Biomed Prev Nutr 2012;2:269-275.

[48] Santana HSR, de Carvalho FO, Silva ER, Santos NGL, Shanmugam S, et al. Anti-inflammatory activity of limonene in the prevention and control of injuries in the respiratory system: a systematic review. Curr Pharm Des 2020;26:2182-2191.

[49] de Souza Pessoa ML, Silva LMO, Araruna MEC, de Lima Serafim CA, Alves Júnior EB, et al. Antifungal activity and antidiarrheal activity via antimotility mechanisms of (-)-fenchone in experimental models. World J Gastroenterol 2020;26:6795-6809.

[50] Him A, Ozbek H, Turel I, Oner AC. Antinociceptive activity of alpha-pinene and fenchone. Pharmacologyonline 2008;3:363-369.

[51] Ali N, Chhetri B, Dosoky N, Shari K, Al-Fahad AJ, et al. Antimicrobial, antioxidant, and cytotoxic activities of Ocimum forskolei and Teucrium yemense (Lamiaceae) Essential Oils. Medicines 2017;4:17.

[52] De Cássia Da Silveira E Sá R, Andrade LN, De Sousa DP. A review on anti-inflammatory activity of monoterpenes. Molecules 2013;18:1227-1254.

[53] Mota AS, Rosário Martins M, Arantes S, Lopes VR, Bettencourt E, et al. Antimicrobial activity and chemical composition of the essential oils of Portuguese foeniculum vulgare fruits. Nat Prod Commun 2015;10:673-676.

[54] Martati E, Akmalina MA. Antioxidant activity and estragole content of ethanolic and methanolic extract of fennel (Foeniculum vulgare mill.) and its risk assessment using Margin of Exposure (MOE). Int Food Res J 2018;25:S43-S49.

[55] Andrade TCB, Lima SGD, Freitas RM, Rocha MS, Islam T, et al. Isolation, characterization and evaluation of antimicrobial and cytotoxic activity of estragole, obtained from the essential oil of croton zehntneri (euphorbiaceae). An Acad Bras Cienc 2015;87:173-182.

[56] Silva-Alves KS, Ferreira-da-Silva FW, Peixoto-Neves D, Viana-Cardoso KV, Moreira-Júnior L, et al. Estragole blocks neuronal excitability by direct inhibition of Na+ channels. Braz J Med Biol Res 2013;46:1056-1063.

[57] Shen Y, Song X, Li L, Sun J, Jaiswal Y, et al. Protective effects of p-coumaric acid against oxidant and hyperlipidemia-an in vitro and in vivo evaluation. Biomed Pharmacother 2019;111:579-587.

[58] Kwiatkowski P, Pruss A, Masiuk H, Mnichowska-Polanowska M, Kaczmarek M, et al. The effect of fennel essential oil and trans-anethole on antibacterial activity of mupirocin against Staphylococcus aureus isolated from asymptomatic carriers. Postep dermatologii i Alergol 2019;36:308-314.

[59] Marín I, Sayas-Barberá E, Viuda-Martos M, Navarro C, Sendra E. Chemical composition, antioxidant and antimicrobial activity of essential oils from organic fennel, parsley, and lavender from Spain. Foods 2016;5(1):5010018.

[60] Shabnam J, Sobia M, Ibatsam K, Rauf A. Comparative antimicrobial activity of clove and fennel essential oils against food borne pathogenic fungi and food spoilage bacteria. African J Biotechnol 2012;11:16065-16070.

[61] Roby MHH, Sarhan MA, Selim KAH, Khalel KI. Antioxidant and antimicrobial activities of essential oil and extracts of fennel (Foeniculum vulgare L.) and chamomile (Matricaria chamomilla L.). Ind Crops Prod 2013;44:437-445.

[62] Ahmed AF, Shi M, Liu C, Kang W. Comparative analysis of antioxidant activities of essential oils and extracts of fennel (Foeniculum vulgare Mill.)seeds from Egypt and China. Food Sci Hum Wellness 2019;8:67-72.

[63] Pacifico S, Galasso S, Piccolella S, Kretschmer N, Pan S-P, et al. Winter wild fennel leaves as a source of anti-inflammatory and antioxidant polyphenols. Arab J Chem 2018;11:513-524.

[64] Mansourabadi AH, Shams A, Mansouri R, Najafi A, Ajami M. Effects of fennel, asafetida and ginseng ethanolic extracts on growth and proliferation of mouse breast cancer 4T1 cell lines. Adv Herb Med 2015;1:34-39.

[65] Bakry S, Mehany ABM. Anti carcinogenic activity of Methanolic Extract of Fennel Seeds (Foeniculum vulgare) against breast , colon , and liver cancer cells. 2016;3:255-266.

[66] El-Garawani IM, El-Nabi SH, Dawoud GT, Esmail SM, Abdel Moneim AE. Triggering of apoptosis and cell cycle arrest by fennel and clove oils in Caco-2 cells: the role of combination. Toxicol Mech Methods 2019;29:710-722.

[67] Ghasemian A, Al-Marzoqi AH, Mostafavi SKS, Alghanimi YK, Teimouri M. Chemical Composition and Antimicrobial and Cytotoxic Activities of Foeniculum vulgare Mill Essential Oils. J Gastrointest Cancer 2020;51:260-266.

[68] Akbari A, Izadi-Darbandi A, Bahmani K. Assessment of phenolic profile, and antioxidant activity in developed breeding populations of fennel (Foeniculum vulgare Mill). Biocatal Agric Biotechnol 2023;48:102639.

[69] Kataoka H, Horiyama S, Yamaki M, Oku H, Ishiguro K, et al. Anti-inflammatory and anti-allergic activities of hydroxylamine and related compounds. Biol Pharm Bull 2002;25:1436-1441.

[70] Choi EM, Hwang JK. Antiinflammatory, analgesic and antioxidant activities of the fruit of Foeniculum vulgare. Fitoterapia 2004;75:557-565.

[71] Reiter M, Brandt W. Relaxant effects on tracheal and ileal smooth muscles of the guinea pig. Arzneimittelforschung 1985;35:408-414.

[72] Chakŭrski I, Matev M, Koĭchev A, Angelova I, Stefanov G. Treatment of chronic colitis with an herbal combination of Taraxacum officinale, Hipericum perforatum, Melissa officinaliss, Calendula officinalis and Foeniculum vulgare. Vutr Boles 1981;20:51-54.

[73] Nassar MI, Aboutabl E sayed A, Makled YA, El-Khrisy ED, Osman AF. Secondary metabolites and pharmacology of Foeniculum vulgare Mill. Subsp. Piperitum. Rev Latinoam Química. 2010;38:103-112.

[74] Cáceres A, Girón LM, Martínez AM. Diuretic activity of plants used for the treatment of urinary ailments in Guatemala. J Ethnopharmacol 1987;19:233-245.

[75] Tanira MOM, Shah AH, Mohsin A, Ageel AM, Qureshi S. Pharmacological and toxicological investigations on Foeniculum vulgare dried fruit extract in experimental animals. Phyther Res 1996;10:33-36.

[76] Bardai SE, Lyoussi B, Wibo M, Morel N. Pharmacological evidence of hypotensive activity of Marrubium vulgare and Foeniculum vulgare in spontaneously hypertensive rat. Clin Exp Hypertens 2001;23:329-343.

[77] Abdul-Ghani AS, Amin R. The vascular action of aqueous extracts of Foeniculum vulgare leaves. J Ethnopharmacol 1988;24:213-218.

[78] Agarwal R, Gupta SK, Agrawal SS, Srivastava S, Saxena R. Oculohypotensive effects of Foeniculum vulgare in experimental models of glaucoma. Indian J Physiol Pharmacol 2008;52:77-83.

[79] Pourjafari F, Haghpanah T, Nematollahi-Mahani SN, Pourjafari F, Ezzatabadipour M. Hydroalcoholic extract and seed of Foeniculum vulgare improve folliculogenesis and total antioxidant capacity level in F1 female mice offspring. BMC Complement Med Ther 2020;20:1-8.

[80] Devi K, Vanithakumari G, Anusya S, Mekala N, Malini T, Elango V. Effect of Foeniculum vulgare seed extract on mammary glands and oviducts of ovariectomised rats. Anc Sci Life. 1985;5(2):129.

[81] Albert-Puleo M. Fennel and anise as estrogenic agents. J Ethnopharmacol 1980;2:337-344.

[82] Özbek H, Uğraş S, Dülger H, Bayram I, Tuncer I, et al. Hepatoprotective effect of Foeniculum vulgare essential oil. Fitoterapia 2003;74:317-319.

[83] Rabeh NM, Aboraya AO, Raheem ZH, Jebor AA, Mohammed SK, et al. Hepatoprotective effect of dill (Anethum graveolens L.) and fennel (Foeniculum vulgare) oil on hepatotoxic rats. Pakistan J Nutr 2014;13:303-309.

[84] Sushruta K, Satyanarayana S, Srinivas S, Sekhar JR. Evaluation

of the blood-glucose reducing effects of aqueous extracts of the selected umbelliferous fruits used in culinary practices. Trop J Pharm Res 2006;5:613-617.

[85] Abou N, El-Soud NHA, El-Laithy N, El-Saeed G, Wahby MS, et al. Antidiabetic activities of Foeniculum vulgare Mill. essential oil in streptozotocin-induced diabetic rats. Maced J Med Sci. 2011;4:139-146.

[86] Joshi H, Parle M. Cholinergic basis of memory-strengthening effect of Foeniculum vulgare Linn. J Med Food 2006;9:413-417.

[87] Omidvar S, Esmailzadeh S, Baradaran M, Basirat Z. Effect of fennel on pain intensity in dysmenorrhoea: A placebo-controlled trial. Ayu 2012;33:311-313.

[88] Bokaie M, Farajkhoda T, Enjezab B, Khoshbin A, Karimi-Zarchi M. Oral fennel (Foeniculum vulgare) drop effect on primary dysmenorrhea: Effectiveness of herbal drug. Iran J Nurs Midwifery Res 2013;18:128-132.

[89] Archer DF, Altomare C, Jiang W, Cort S. Ospemifene's effects on lipids and coagulation factors: A post hoc analysis of phase 2 and 3 clinical trial data. Menopause 2017;24:1167-1174.

[90] Mahdavian M, Mirzaii Najmabadi K, Hosseinzadeh H, Mirzaeian S, Badiee Aval S, et al. Effect of the mixed herbal medicines extract (fennel, chamomile, and saffron) on menopause syndrome: a randomized controlled clinical trial. J caring Sci 2019;8:181-189.

[91] Bae J, Kim J, Choue R, Lim H. Fennel (Foeniculum vulgare) and Fenugreek (Trigonella foenum-graecum) tea drinking suppresses subjective short-term appetite in overweight women. Clin Nutr Res 2015;4:168.

[92] Akha O, Rabiei K, Kashi Z, Bahar A, Zaeif-Khorasani E, et al. The effect of fennel (Foeniculum vulgare) gel 3% in decreasing hair thickness in idiopathic mild to moderate hirsutism, A randomized placebo controlled clinical trial. Casp J Intern Med 2014;5:26-29.

[93] Manohar R, Ganesh A, Abbyramy N, Abinaya R, Balaji SK, et al. The effect of fennel seeds on pH of saliva - A clinical study. Indian J Dent Res Off Publ Indian Soc Dent Res. 2020;31:921-923.

[94] Di Ciaula A, Portincasa P, Maes N, Albert A. Efficacy of bio-optimized extracts of turmeric and essential fenneoil on the quality of life in patients with irritable bowel syndrome. Ann Gastroenterol 2018;31:685-691.

[95] Alazadeh M, Azadbakht M, Niksolat F, Asgarirad H, Moosazadeh M, et al. Effect of sweet fennel seed extract capsule on knee pain in women with knee osteoarthritis. Complement Ther Clin Pract 2020;40:101219.