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REVIEW

Foeniculum vulgare: A comprehensive review of its traditional use, phytochemistry, pharmacology, and safety

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Abstract *Foeniculum vulgare* (Apiaceae) commonly known as fennel is a well known and important medicinal and aromatic plant widely used as carminative, digestive, lactogogue and diuretic and in treating respiratory and gastrointestinal disorders. Its seeds are used as flavourings in baked goods, meat and fish dishes, ice cream, alcoholic beverages and herb mixtures. Phenols, phenolic glycosides and volatile aroma compounds such as trans-anethole, estragole and fenchone have been reported as the major phytoconstituents of this species. Different pharmacological experiments in a number of *in vitro* and *in vivo* models have convincingly demonstrated the ability of *F. vulgare* to exhibit antifungal, antibacterial, antioxidant, antithrombotic and hepatoprotective activities, lending support to the rationale behind several of its therapeutic uses. Phenolic compounds isolated from *F. vulgare* are considered to be responsible for its antioxidant activity while the volatile aroma compounds make it an excellent flavouring agent. The present review is an up-to-date and comprehensive analysis of the chemistry, pharmacology, traditional uses and safety of *F. vulgare*.
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Contents

1. Introduction

Foeniculum vulgare Mill. is a biennial medicinal and aromatic plant belonging to the family Apiaceae (Umbelliferaceae). It is a hardy, perennial–umbelliferous herb with yellow flowers and feathery leaves. It grows to a height of up to 2.5 m with hollow stems. The leaves grow up to 40 cm long; they are finely dissected with the ultimate segments filiform (thread like) of about 0.5 mm wide. The flowers are produced in terminal compound umbels. The fruit is a dry seed 4–10 mm long. It is generally considered indigenous to the shores of Mediterranean Sea but has become widely naturalised in many parts of the world especially on dry soils near the sea coast and on the river banks. Some authors distinguish two sub-species of fennel, *piperitum* and *vulgare*: sub-species *piperitum* has bitter seeds, while sub-species *vulgare* has sweet seeds which are used as flavouring agents in baked goods, meat and fish dishes, ice creams, alcoholic beverages, etc due to their characteristic anise odour (Diaaz-Maroto et al., 2006). Morphological differences between these two sub-species are not always clearly defined.

2. Culinary uses

It is a highly aromatic and flavourful herb with culinary and medicinal uses. Fennel seeds are anise like in aroma and are used as flavourings in baked goods, meat and fish dishes, ice cream, alcoholic beverages and herb mixtures (Diaaz-Maroto et al., 2005). The bulb, foliage and seeds of the fennel plant are widely used in many of the culinary traditions of the world. Dried fennel seed is an aromatic, anise-flavoured spice, brown or green in colour when fresh, slowly turning a dull grey as the seed ages. For cooking green seeds are the best. The bulb is a crisp, hardy root vegetable and may be sautéed, stewed, braised, grilled or eaten raw. Fennel features predominantly in Mediterranean cuisine, where bulbs and fronds are used, both raw and cooked, in side dishes, salads, pastas, vegetable dishes. Many cultures in the Indian subcontinent and the Middle East use fennel seeds in their cooking. Fennel is one of the most important spices in Kashmiri Pandit and Gujarati cooking (Grieve, 1931).

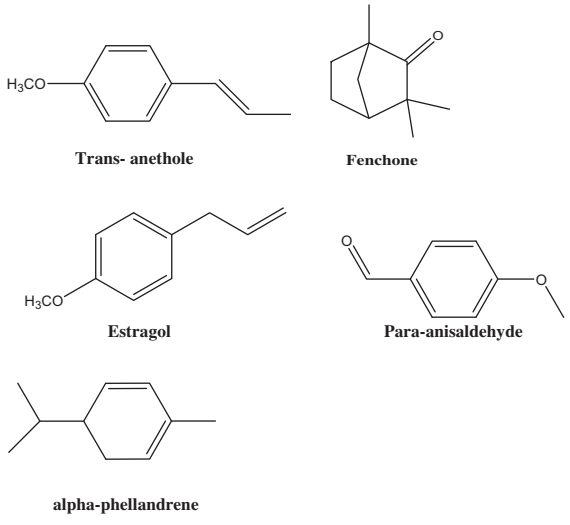

Figure 1 The molecular structures of the major bioactive essential oil components of *Foeniculum vulgare*.

3. Use in local and traditional medicine

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 liquorice powder. Fennel water has properties similar to those of anise and dill water: mixed with sodium bicarbonate and syrup, these waters constitute the domestic 'gripe water', used to correct 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 a potential use in the treatment of glaucoma, as a diuretic and a potential drug for the treatment of hypertension. It has been used as a galactagogue improving the milk supply of a breast feeding mother. This is suggested to be due to the presence of phytoestrogens present in fennel which promote growth of breast tissue (Agarwal et al., 2008).

The objective of this review article is to present the existing knowledge of *F. vulgare's* phytochemical composition, its culinary uses, use in local medicine, and reported *in vitro* and *in vivo* pharmacological studies on plant-derived extracts, isolated phytochemicals and also to highlight the potential for developing evidence-based *F. vulgare* preparations.

4. Phytochemistry

F. vulgare has been reported to contain 6.3% of 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.

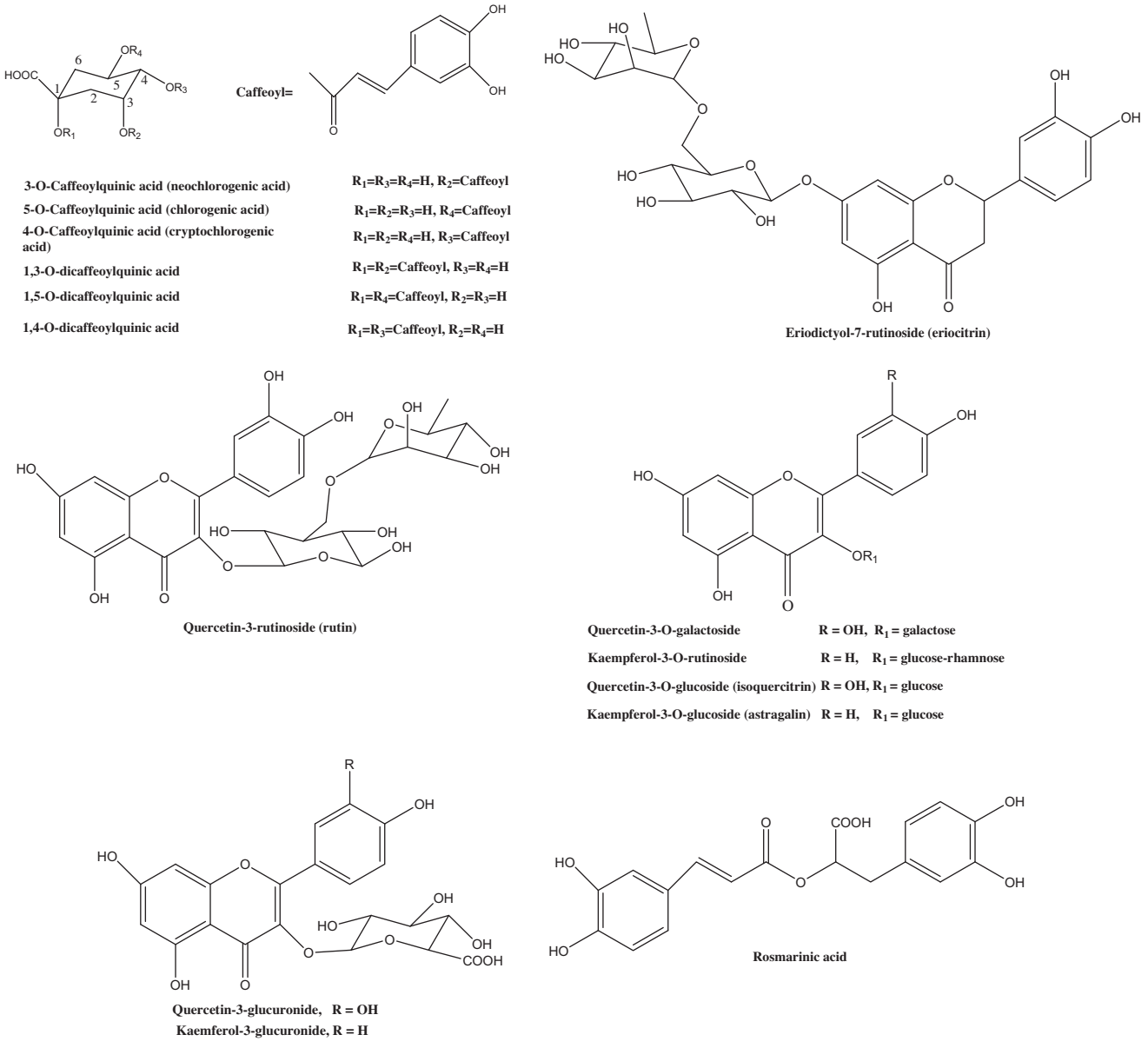

Figure 2 Molecular structures of some phenols and phenolic glycosides isolated from *Foeniculum vulgare*.

4.1. Essential oil

F. vulgare is well known for its essential oil. The characteristic anise odour of *F. vulgare* which is due to its essential oil makes it an excellent flavouring agent in baked goods, meat and fish dishes, ice-cream and alcoholic beverages. The major components of *F. vulgare* seed essential oil have been reported to be trans-anethole, fenchone, estragol (methyl chavicol), and α-phellandrene, their molecular structures are shown in Fig. 1. The relative concentration of these compounds varies considerably depending on the phonological state and origin of the fennel (Diaaz-Maroto et al., 2006). The essential oil composition of *F. vulgare* exhibits considerable chemodiversity depending upon the method of extraction and geographical origin. The accumulation of these volatile compounds inside the plant is variable, appearing practically in any of its parts viz. roots, stem, shoots, flowers and fruits (Diaaz-Maroto et al., 2006; Gross et al., 2009). In one study it was reported that the essential oil content and composition varies during the different maturation stages of *F. vulgare*. The essential oil content was reported to decline with fruit maturity. The content of trans-anethole, the main component, varied between 81.63% and 87.85% (Telci et al., 2009). Another study reported that the phenylpropenes estragol and trans-anethole which are the major constituents of the oleoresin of the aerial parts of *F. vulgare* varied during plant development, these two compounds being maximal in flowers and developing mericarps. The pharmacological effects of the *F. vulgare* fruits are generally attributed to their essential oil. Numerous studies have shown that the essential oil and its individual constituents exhibit novel pharmacological activities. (+) Fenchone and P-anisaldehyde were identified as the major acaricidal agents against *Dermatophagoides farinae* and *Dermatoghagoides pteronyssinus*. Hence these compounds can be used as potential house dust mite control agents or as lead compounds. In another study, anethole has been reported to be active oestrogenic agent. However, in some studies it has been shown that polymers of anethole i.e. dianethole and photoanethole are the actual oestrogenic agents. Anethole has been also reported to be a safe antithrombotic agent due to its antiplatelet activity, clot destabilising effect and vaso-relaxant action (Tognolini et al., 2007). However, estragole, a main component of *F. vulgare* has become a cause of concern, as the structurally similar methyleugenol has been recently found to be a potential carcinogen. This has led to the European Union (EU) to allow a new legal limit for estragole of 10 mg/kg in non-alcoholic beverages (Zeller and Rychlik, 2006).

The other classes of phytochemicals present in *F. vulgare* are phenols and phenolic glycosides, the chemical structures of some of these phytochemicals are shown in Fig. 2. The structures of some of the flavonoid aslycones and miscellaneous compounds are given in Figs. 3 and 4. *F. vulgar*e has been reported to contain phenolic acids like 3-O-Caffeoylquinic acid, 4-O-caffeoylquinic acid, 5-O-caffeoylquinic acid, 1,3-O-di-caffeoylquinic acid, 1,4-O-di-caffeoylquinic acid, 1,5-O-di-caffeoylquinic acid. The flavonoids like eriodictyol-7-rutinoside, quercetin-3-rutinoside and rosmarinic acid have also been isolated from *F. vulgare* (Faudale et al., 2008; Park, 1996). Quercetin-3-O-galactoside, kaempferol-3-O-rutinoside and kaempferol-3-O-glucoside have also been reported to occur in the aqueous extract of *F. vulgare*. Quercitin-3-O-glucuronide, kampferol-3-O-glucuronide, isoquercitin and isorhamnetin-3-O-glucoside have also been isolated from *F. vulgare* Parejo et al., 2004a). The phenolic compounds present in *F. vulgare* are considered to be associated with the prevention of diseases thought to be induced by oxidative stress such as cardiovascular diseases, cancer and inflammation. These phenolic compounds have received tremendous attention among nutritionists, food scientists and consumers due to their roles in human health. Diglucoside stilbene trimers and benzoisofuranone derivatives have also been isolated from *F. vulgare* fruit together with cis-miyabenol C, trans-miyabenol C, trans-resveratrol-3-O-β-D-glucopyranoside, sinapyl glucoside, syringin-4-O-β-glucoside, oleanolic acid, 7α-hydroxycampesterol, (3β,5α,8α,22E) 5,8-epidioxy-ergosta-6,22-dien-3-ol, and 2,3-dihydropropylheptadec-5-onoate (Marino et al., 2007).

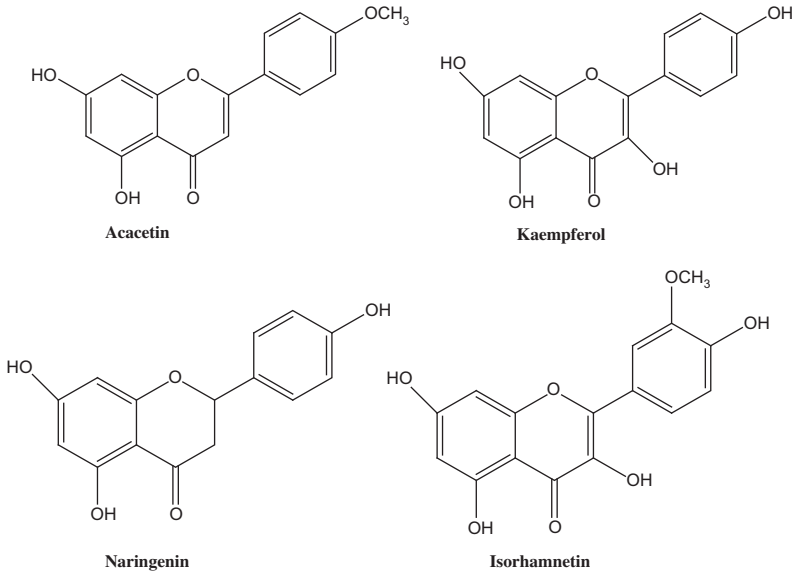

Figure 3 Molecular structures of some flavonoid aglycons reported in *Foeniculum vulgare*.

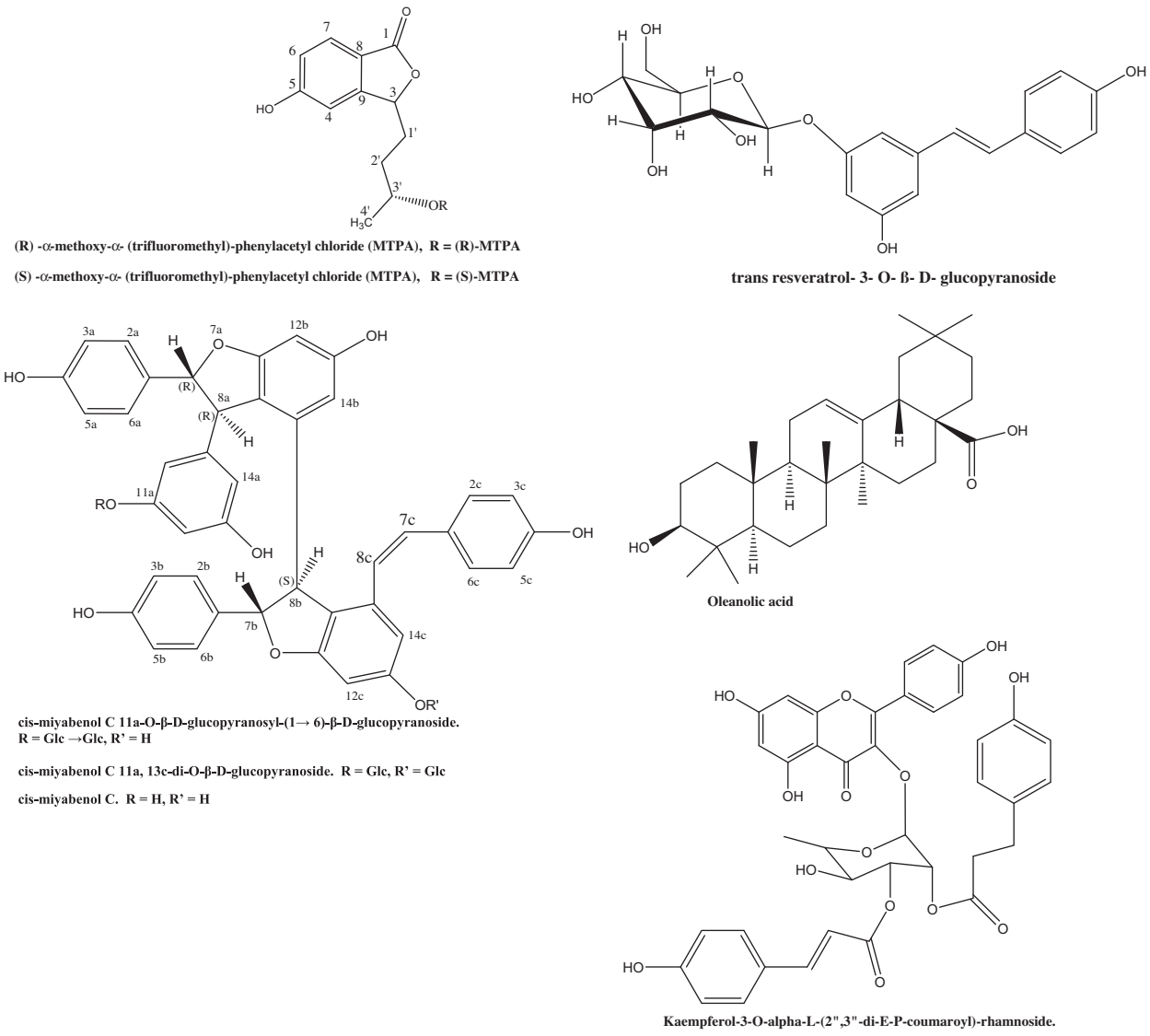

Figure 4 Molecular structures of some miscellaneous compounds isolated from *Foeniculum vulgare*.

An acylated kaemferol glycoside from flowers of *F. vulgare* has also been isolated (Soliman et al., 2002) (see Figs. 3–5).

5. Pharmacology

5.1. Antibacterial activity

The essential oil extracted from the fruits of *F. vulgare* exhibited antibacterial effect against foodborne pathogens such as *Escherichia coli*, *Bacillus megaterium* and *Staphylococcus aureus* (Mohsenzadeh, 2007), *E. coli* 0157:H7, *Listeria monocytogenes* and *S. aureus* (Dadalioglu and Evrendilek, 2004; Cantore et al., 2004). Aqueous and organic extracts of *F. vulgare* have been reported to show antibacterial activity against some bacterial strains (Kaur and Arora, 2008). The seed essential oil of *F. vulgare* has also been reported to possess antibacterial activity against some human pathogenic bacteria. Ethanol and water extracts of *F. vulgare* have shown activity against *Campylobacter jejuni* and *Helicobacter pylori* (Mahady et al., 2005). In another study, the *F. vulgare* essential oil has been shown to exhibit potential for the control of multidrug resistant *Acinetobacter baumannii* infections. Some chemical constituents from *F. vulgare* have been identified as active antimicrobial principles such as a phenyl propanoid derivative – Dillapional was found to be the active antimicrobial principle of the *F. vulgare* stem. Another molecule – Scopoletin which is a coumarin derivative has been isolated from *F. vulgare* and reported to possess marginal antimicrobial effect (Kwon et al., 2002).

5.2. Antifungal activity

The fennel essential oil has been reported to exhibit antifungal effect. The fennel essential oil and its seed extracts have been reported to exhibit antimycobacterial and anticandidal activity (Abed, 2007). Various bark extracts of *F. vulgare* have also been reported to possess antifungal activity against *Candida albicans* (Pai et al., 2010). The essential oil of *F. vulgare* has

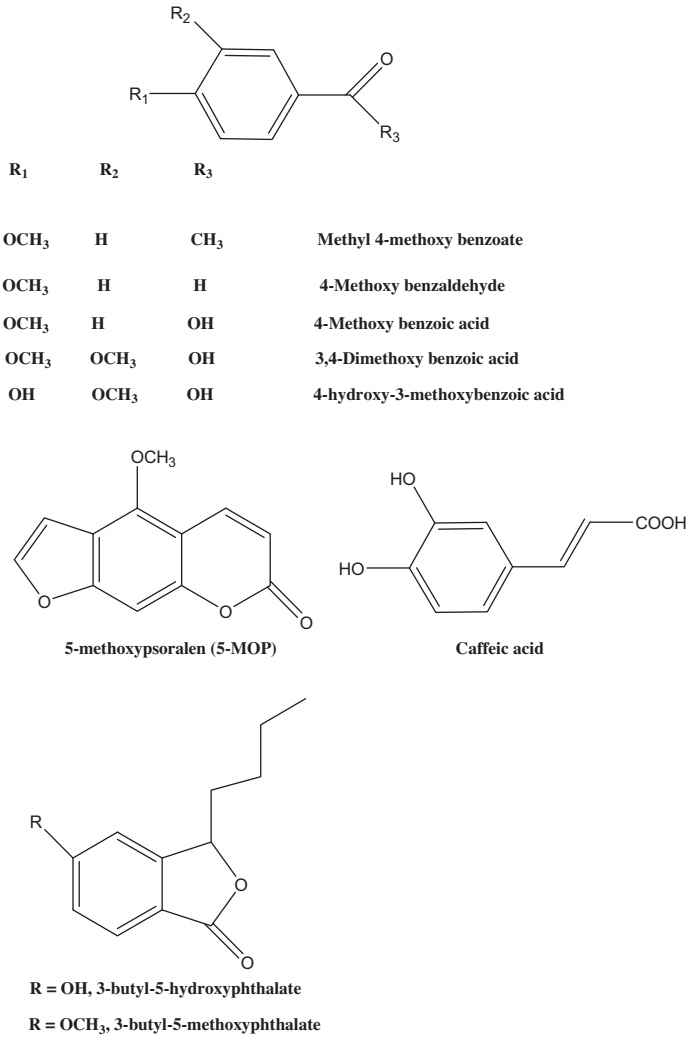

Figure 5 Molecular structures of bioactive compounds from the methanol extract of *F. vulgare* seeds. These compounds have been reported to possess human liver cytochrome P 450 3A4 inhibitory activity with 5-methoxypsoralen showing the strongest inhibition.

also been reported to reduce the mycelial growth and germination of *Sclerotinia sclerotiorum* and as such could be used as bio fungicide alternative to synthetic fungicides against phytopathogenic fungi (Soylu et al., 2007). The essential oil of *F. vulgare* has been reported to show complete zone of inhibition against *Aspergillum niger*, *Aspergillum flavus*, *Fusarium graminearum* and *Fusarium moniliforme* at 6 µl dose (Singh et al., 2006).

5.3. Antioxidant activity

The antioxidant activity of wild, edible and medicinal fennels from different Mediterranean countries has been determined. Wild fennel has been found to exhibit a radical scavenging activity higher than that of both medicinal and edible fennels (Faudale et al., 2008). The methanolic extract of *F. vulgare* fruit has also been reported to exhibit antioxidant activity by decreasing the malondialdehyde level in *F. vulgare* fruit methanol extract group compared to the control group. The essential oil and acetone extracts of *F. vulgare* have been reported to exhibit strong antioxidant activity in comparison with butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) (Ruberto et al., 2000). The inhibitory action of oil and the acetone extracts in linoleic acid system was studied by monitoring peroxide accumulation in emulsion during incubation through ferric thiocyanate method. *F. vulgare* fruit extract and the purified compounds namely cis-miyabenol C 11a-O-β-D-glucopyranosyl-(1→6)-β-D-glucopyranoside, cis-miyabenol C, trans-miyabenol C, sinapyl glucoside and syringing 4-O-β-glucoside have been reported to exhibit antioxidant activity. The n-BuOH extract of the *F. vulgare* fruit showed a moderate activity in the lipid peroxidation assay but strong activity at the higher tested concentration. Pure compounds isolated from *F. vulgare* showed higher antioxidant activity than the crude extracts (Marino et al., 2007).

The isolated phenolic compounds from the residue of flowering aerial parts of the bitter fennel resulting from its distillation for essential oils have been reported to possess strong antiradical scavenging activity which may contribute to the interpretation of the pharmacological effect of *F. vulgare*. The isolated compounds were characterised as 3-caffeoylquinic acid, 4-caffeoylquinic acid, 1,5-O-dicaffeoylquinic acid, ros-

marinic acid, eriodictyol-7-rutinoside, quercetin-3-O-galactoside, kaempferol-3-O-rutinoside and kaempferol-3-O-glucoside. (Parejo et al., 2004b). In another study water and ethanol extracts of *F. vulgare* seeds have been reported to display antioxidant activity. 100 μg of water and ethanol extracts exhibited 99.1% and 77.5% inhibition of peroxidation in linoleic acid system respectively and greater than the same dose of α-tocopherol (36.1%). Both extracts were reported to have effective reducing power, free radical scavenging, superoxide anion radical scavenging, hydrogen peroxide scavenging and metal chelating activities. Essential oils of the fruits of three organically grown cultivars of Egyptian fennel (*F. vulgare* var. *azoricum*, *F. vulgare* var. *dulce* and *F. vulgare* var. *vulgare*) were reported to possess antioxidant activity. Essential oils from the *azoricum* and *dulce* cultivars were more effective antioxidants than those from the *vulgare* cultivar (Shahat et al., 2011).

5.4. Antithrombotic activity

The essential oil of *F. vulgare* and its main component, anethole has been shown to have a safe antithrombotic activity that originates due to their broad-spectrum antiplatelet activity, clot destabilizing effect and vasorelaxant action. Anethole, the main component of fennel oil tested in guinea pig plasma was as potent as the fennel oil in inhibiting arachidonic acid, collagen-ADP and U46619 induced aggregation. Anethole also prevented thrombin induced clot reaction at concentrations similar to fennel oil. The fennel oil and anethole were tested in rat aorta with or without endothelium and displayed comparable NO-independent vasorelaxant activity at antiplatelet concentrations which have been proved to be free from cytotoxic effects *in vitro*. Furthermore, both *F. vulgare* essential oil and anethole (100 mg/kg oral administration) provided significant protection towards ethanol induced gastric lesions in rats (Tognolini et al., 2007).

5.5. Anti-inflammatory activity

Oral administration (200 mg/kg) of *F. vulgare* fruit methanolic extract has been reported to show inhibitory effects against acute and subacute inflammatory diseases and type IV allergic reactions (Choi and Hwang, 2004).

5.6. Oestrogenic activity

F. vulgare has been used as an oestrogenic agent for centuries. It has been reported to increase milk secretion, promote menstruation, facilitate birth, alleviate the symptoms of the male climacteric and increase libido. The main constituent of fennel essential oil, anethole has been considered to be the active oestrogenic agent. Some other studies have suggested that the actual pharmacologically active agents are polymers of anethole, such as dianethole and photoanethole (Albert-puleo, 1980).

5.7. Hepatoprotective activity

The fennel essential oil has been reported to possess hepatoprotective activity. In a study, the hepatotoxicity produced by acute CCl_4 administration was found to be inhibited by fennel essential oil with evidence of decreased levels of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and bilirubin (Ozbek et al., 2003).

5.8. Antidiabetic activity

The essential oil of *F. vulgare* has been reported to show hypoglycaemic activity in Streptozotocin induced diabetic rats. Ingestion of essential oil of *F. vulgare* to diabetic rats corrected the hyperglycaemia from (162.5 + 3.19 mg/dl) to (81.97 + 1.97 mg/dl) and the activity of serum glutathione peroxidise from (59.72 + 2.78 u/g Hb) to (99.60 + 6.38 u/g Hb). This makes the possibility of its inclusion in antidiabetic drug industry (El-Soud et al., 2011).

5.9. Miscellaneous

5.9.1. In vitro cytoprotection and antitumour activity

The methanolic extract of *F. vulgare* has been reported to exhibit *in vitro* cytoprotective activity against normal human blood lymphocytes by micronucleus assay and anti-tumour activity against B16F10 melanoma cell line by trypan blue exclusion assay for cell viability. Lymphocyte culture treated with 70% methanolic extract of *F. vulgare* showed very less percentage of micronucleus i.e. 0.006% as compared to standard drug doxorubicin which showed 0.018% micronucleus. On the other hand 70% methanolic extract of *F. vulgare* showed good anti-tumour activity at the concentration of 200 μg/ml. This suggests that *F. vulgare* could be considered as a natural resource of antitumour agents as well as cytoprotective to normal cells (Pradhan et al., 2008).

5.9.2. Acaricidal activity

F. vulgare fruit oil has been reported to possess acaricidal activity against *D. farinae* and *D. pteronyssinus* using direct contact application and compared with that of the commercial repellent benzyl benzoate. The biologically active constituents of the *F. vulgare* fruit oil have been identified as P-anisaldehyde, (+)-fenchone, (−)-fenchone, thymol and estragol (Lee, 2004).

The methanol extract of *F. vulgare* fruit has been reported to exhibit mosquito repellent activity against *Aedes aegypti* females using skin and patch tests. The biologically active constituents of the *Foeniculum* fruits were characterised as (+)-fenchone and (z)-9-octadecanoic acid (Kim et al., 2002).

5.9.3. Antihirustism activity

The ethanolic extract of *F. vulgare* has been reported to display antihirustism activity. In a double blind study patients were treated with creams containing 1%, 2% of fennel extract and placebo. The cream containing 2% fennel is better than the cream containing 1% fennel (Javidnia et al., 2003).

5.9.4. Effect on uterine contraction

The effects of fennel essential oil on the uterine contraction in rats have been reported. Administration of different doses of fennel essential oil reduced the intensity of oxytocin and PGE_2 induced contractions significantly (25 and 50 μg/ml for oxytocin and10 and 20 μg/ml for PGE_2 respectively). Fennel

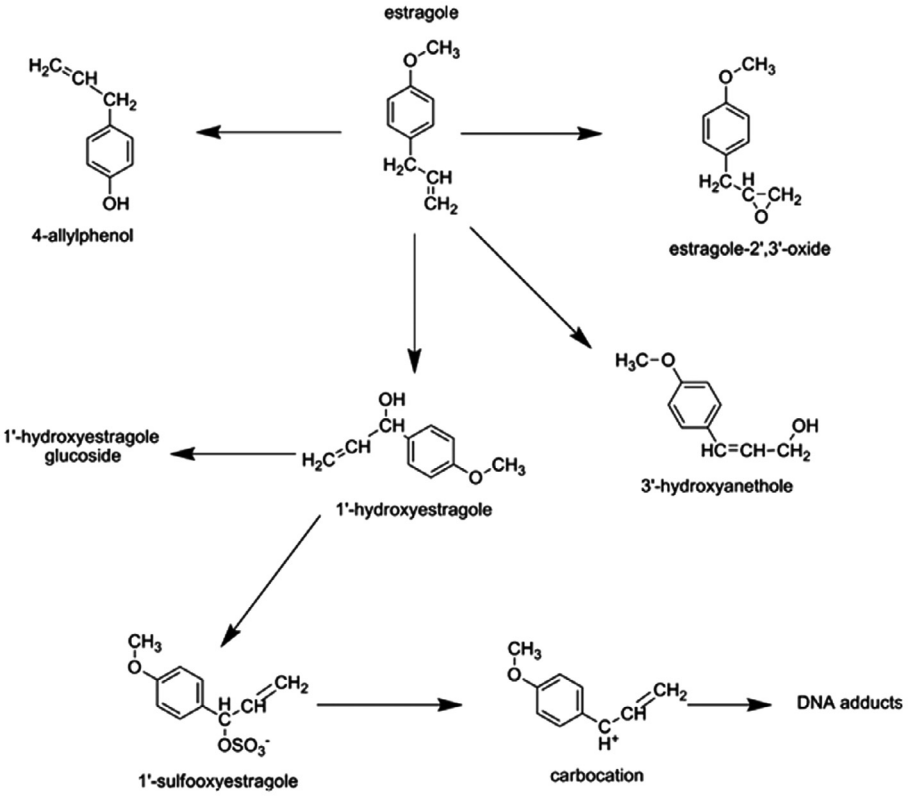

Figure 6 Metabolism of estragole (suggested biotransformation of estragole in experimental animals leading to the formation of mutagenic metabolites (adapted from Punt et al., 2008).

essential oil also reduced the frequency of contractions induced by PGE_2 but not with oxytocin. The estimated LD_{50} obtained in female rats by moving average method was 1326 mg/kg. Furthermore, no obvious damage was observed in the vital organs of the dead animals (Ostad et al., 2001).

5.9.5. Human liver cytochrome P450 3A4 inhibitory activity

Thirteen compounds isolated from the methanolic extract of fennel have been found to possess human liver cytochrome P450 3A4 inhibitory activity. Among these compounds (Fig. 5) 5-methoxypsoralen (5-MoP) showed the strongest inhibition with an IC_{50} value of 18.3 μM and with a mixed type of inhibition. (Subehan et al., 2007).

6. Safety

The safety of medicinal and spice plants and of their preparations deserves increased scientific attention. One of the main conditions for use of herbal preparations in medicinal conditions is the absence of such risks as mutagenicity, carcinogenicity, and teratogenicity. In general, such products need to have minimal toxicity and side effects. Generally, the vast majority of herbal remedies are recognised as safe, and individual hypersensitivity is usually considered as the most common but controllable risk. However, for those individual compounds exhibiting toxic effects in laboratory animals, the question of possible negative effects in humans remains open. In the case of *F. vulgare* some compounds have come under scrutiny, most importantly, estragole.

Estragole (Methylchavicol) is one of the main components of the essential oil of *F. vulgare*. It has been reported that estragole is associated with the development of malignant tumours in rodents. This was the basis for the recommendations of the Scientific Committee on Food (SCF) of the European Union to restrict the use of this substance (Opinion of the Scientific Committee on Estragole, 2001) but the potential of estragole to induce carcinogenesis in humans remains unclear. The ability of estragole to cause genotoxicity and, thus, to be carcinogenic was first described by Drinkwater (Drinkwater et al., 1976) and then followed by numerous *in vivo* and *in vitro* studies (Swanson et al., 1979, 1981; Miller et al., 1983; Miller and Miller, 1983; Paini et al., 2010). It was found that estragole possesses tissue-, species-, and sex-specific carcinogenic effects. According to recent evidence, estragole does not have a direct carcinogenic action. The essential factor for estragole's carcinogenicity is its metabolic activation, leading to the formation of unstable molecules and active radicals that form adducts with nucleic acids and thus damage DNA (Phillips, 1994). Estragole metabolism (Fig. 6) is dose-dependent and elevated doses of estragole increase its biotransformation, leading to the formation of mutagenic metabolites (Punt et al., 2008). The biotransformation of the same substance can differ in animals and in humans, which raises the question of whether the mutagenic metabolites of estragole are formed in humans.

7. Conclusion

F. vulgare is a medicinal and aromatic plant with a diverse pharmacological spectrum and having considerable impor-

tance in particular to food industry. Its aroma active compounds such as anethole (and its polymers like dianethole and photoanethole) estragole, (+)-Fenchone and P-anisaldehyde have been recognised as the biologically active molecules possessing oestrogenic, acaricidal and antithrombotic activities. The phenolic molecules present in fennel have been shown to possess potent antioxidant activity in a number of experiments. These bioactive molecules in fennel can be developed as novel pharmacological lead molecules provided their bioavailability, pharmacokinetics, physiological pathways, and importance to human health are known with sufficient detail.

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