Review of the traditional uses, phytochemistry, pharmacology and toxicology of giant fennel (Ferula communis L. subsp. communis)

Maryam Akaberi 1, Milad Iranshahy 1, Mehrdad Iranshahi 1*

1 Biotechnology Research Center, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

Introduction

The genus Ferula (Apiaceae) with about 170 species, mostly occurs throughout central Asia, the Mediterranean region and Northern Africa. Ferula spp. has a long history of medicinal use and their pharmacological effects are well documented in both the human and animal studies. A large number of compounds have been identified in this genus. These include sesquiterpenes (1, 2), sesquiterpene coumarins (3-5), sesquiterpene lactones (6) and sulfur-containing compounds (7-10).

Ferula communis L. subsp. communis (Giant fennel) is a latex-containing perennial plant, 1-2.5 m high, odoriferous, with dense roots. Its cylindrical peduncle is green, striated, with slimy exudate. The branches, 8-10 cm long, are alternate (inferior) or opposite (superior). The leaves are glabrous, with a large sheath. The inflorescence is attached on the terminal part of the peduncle. The plant, despite the name, is not a type of fennel proper belonging to the other genus Foeniculum. The name of the phenolic compound ferulic acid, which can be isolated from giant fennel, is derived from the Latin name of the plant.

Two chemotypes of Ferula communis L. have been characterized with different biological effects. Poisonous chemotype contain mainly prenyl coumarins such as ferulenol (1) and related compounds that are responsible for ferulosis (a lethal haemorrhagic disorder which mainly affects goats, sheep, cattle, and horses) and its toxicity. The other chemotype is non-poisonous and contains daucane esters (11, 12). Genetically, these two chemotypes are different and distributed in different geographic regions (13). Non-poisonous plant is used traditionally as a hormonal plant because of its phytoestrogens content, while the poisonous one may cause different intoxication and even death (14).
In the present paper, we aimed to review the traditional uses, pharmacology, phytochemistry and toxicology of this ancient medicinal plant. All related available information on *F. communis* was collected via electronic search (using Pubmed, SciFinder, Scirus, Embase, Google Scholar, Scopus, Cochrane Library and Web of Science) without time limit.

**Traditional uses**

*F. communis* has traditionally been used as anti-hystera and for the treatment of dysentery (15, 16). The rhizomes of this plant which is known as Alkalakh in Saudi Arabia are used locally as a traditional remedy for the treatment of skin infections, while the roasted flower buds are used against fever and dysentery (17).

Traditional uses of non-poisonous *F. communis* as phytohormone are attributed to ferutinin (21), an aromatic ester of a daucane alcohol. It has been reported that this plant acts as a possible source of phytoestrogens of the daucane type. In Morocco, *F. communis* has traditionally been used as a hypoglycemic medicinal plant (18) but its use has been restricted due to its toxicity.

In traditional medicinal books such as Dioscorides, numerous beneficial applications have been reported for this plant. For example, administration of mashed fresh kernel is useful for expulsion of oral bloody humor, and for the treatment of stomachache with diarrhea. It is also recommended for the treatment of snakebite. Preparation of the crushed plants in the form of wick seal bleeding of the bleeding organ. Administration of plant seeds improves cramps, and if rubbing the combination of mashed seeds with oil on the skin, causes perspiration (19).

**Phytochemistry**

Out of all compounds identified in *F. communis*, sesquiterpene and their derivatives (11, 20, 21), sesquiterpene coumarins (22) and prenylated sesquiterpene coumarins are found abundantly (11, 23, 24).

Investigations on *F. communis* have shown that each of the two identified chemotypes has their own major phytochemicals: one chemotype contains sesquiterpene daucane esters, and the other one is dominated by prenylated coumarins (20, 21).

To consider the chemical differences between two chemotypes of *F. communis*, Arnoldi et al (13), studied daucanes and coumarins of two chemotypes using HPLC-DAD-UV, HPLC-ESI-MS and HPLC-APCI-MS analyses. The chromatogram of non-poisonous chemotype showed two main peaks attributed to ferutinin (21) and the prenylated coumarin ferulenol (1) as well as 10 minor peaks contributing to daucane esters including lapiferin (43) and jaeskeanadiol benzoate (ferutinol benzoate) (66). The chromatogram of poisonous chemotype was totally different from the non-poisonous one. Five main peaks were detected possessing a 4-hydroxycoumarin structure. This chemotype was reported to contain the toxic coumarins ferulenol (1) and its ω-hydroxy derivatives (25). Daucane derivatives could not be detected in the ‘poisonous’ chemotype of *F. communis* (13).

Not only have phytochemical studies been established on various chemotypes of *F. communis*, but several studies also have investigated the major compounds in different plant parts. Studying the fruits of *F. communis* showed that prenylated coumarins were absent, whereas sesquiterpenoid esters, such as the phenylpropane laserin (79) (26) and the daucane ester of anisate (45) were present (20, 26). The fruits from the plants containing prenylated coumarins in their roots and leaves gave in fact a series of 1-oxojaeskeanadiol esters. The major constituent of the fruits was a crystalline mixture of the 5-(O)-angeloyl (46) and isovaleroyl (47) esters of 1-oxojaeskeanadiol. Also, the 5-O-anisoyl ester of 1-oxojaeskeanadiol (48), was obtained from the more polar fractions (26).

**Sesquiterpene coumarins (prenylated coumarins)**

*Ferula* is a genus rich in coumarins, particularly sesquiterpene coumarins (27-29). To date, many sesquiterpene coumarins have been identified from this genus (29). In Figure 1, the chemical structures of sesquiterpene coumarins of this species that have been reported to date, are depicted. Ferulenol (1) is the most abundant and the first coumarin isolated from this species (30). Biological activities of ferulenol have been investigated in several studies (31). In 1986, Valle *et al* isolated two 4-hydroxycoumarin derivatives bearing a farnesyl [(ferulenol (1)] and a 12-hydroxy farnesyl residue (2) at C-3 from the latex of *F. communis* (20). In a separate study, these two compounds were isolated from the root sap of *F. communis* var. *genuina* with haemorrhagic activity and toxicity (25). Derivatives of prenylated coumarins ferulenol and ferprenin (3) (a pyranocoumarin) (24) with functional groups hydroxyl, acetoxy, aldehydic carbonyl at the end of the prenyl residue, have also been isolated from the poisonous chemotype of *F. communis* (11).

Some other sesquiterpene coumarins reported from *F. communis* include samarcandin (22), two new cyclic farnesylcoumarins (4, 5), isoferprenin (6) (32), 2-nor-1,2-secoferulenol (53), feselol (7) and colladonin (8) (21, 34).

Further investigation on aerial parts of *F. communis* grown in Saudi Arabia led to the identification of three compounds namely umbelliferone (15), umbelliprenin (16), and famesiferol A (17) (35). The mentioned compounds have been reported from other *Ferula* Species (36, 37), however, the scientific name of plant used in that study needs to be confirmed by
Further investigation. To our knowledge, *F. communis* is a Mediterranean species of *Ferula* and there is no another document that confirms the presence of *F. communis* in Saudi Arabia.

**Daucane sesquiterpene esters**

A large number of daucane sesquiterpene esters have been isolated from *F. communis* with a 1,5-trans-fused daucane ring system. For instance, Minski et al isolated a number of (21-37) daucane sesquiterpenes from the benzene extract of the dried roots of *F. communis* subsp. *communis* (21). Their further investigation on this plant led to the identification of the daucane ester 14-p-anisoyloxy-dauc-4,8-diene (69), fercomin (50), and fercolide (51) (daucane-γ-lactone) which is the first daucane-γ-lactone identified (21, 38). Daucane esters including compounds 22, 52-54 were also reported from this species (20). Daucane esters (55-61) from leaves and seeds of *F. communis var. breuzfolia* have been reported which are related to jaeschkeanadiol (67) (39). The major constituent of the fruits was a crystalline mixture of the 5-(O)-angelyol (62) and isovaleryl (63) esters of 1-oxoaeschkeanadiol (39). In addition, 5-(O)-anisoyl ester of 1-oxoaeschkeanadiol (64), was identified from more polar fractions (39). Compound 63 had previously been isolated as the oil from a plant of the Asteraceae family (17).

Investigation of *F. communis* rhizomes, using a bioautography-guided isolation technique, has led to the isolation and characterization of three antibacterial sesquiterpenes, namely, the daucane ester 14-(O-hydroxycinnamomoyloxy)-dauc-4,8-diene (65), 2a-acetyl-6a- (benzoyl) jaeschkeanadiol (66) and 2a-acetyl-6a-(p-anisoyl)-jaeschkeanadiol (67) (40).

In a recent work, three daucane sesquiterpenes including acetoxyferutinin, ooxoaeschkeanadiol anisate (48) and ferutidin (22), together with ferulanol, have also been identified from the aerial parts of *F. communis* (31).

**Volatile constituents of *F. communis***

A number of studies have reported the chemical composition of *Ferula* essential oils (41, 42). In a study on *F. communis* leaf oil, forty seven components were identified. The main constituents were myrcene (53.5%) and aristolene (8.5%) (43), however, the oil contained a high content of monoterpenes. In addition, two main sesquiterpenes including, aristolene (8.5%) and (E,E)-farnesol (4.3%), were also present in the volatile oil (43). Chemical composition of essential oils from different parts of the plant showed that the content of aristolene reached 19.0% in leaf oil, while it was absent in flower oil. In contrast, the chemical composition of samples obtained from peduncle was different and dominated by sesquiterpenes. The sesquiterpenes aristolene, β-gurjunene, α- and β-selinenes were the major components of the essential oil of peduncle. It is notable that the yields of peduncle oil were at least two times lower than those of leaf and flower oils (43).

The study of the chemical composition of the oil from flower-heads using a carbon dioxide supercritical extraction (SPE) (44) showed that the main constituents in the oil were α-gurjunene, β-gurjunene, α-selinene and β-selinene. The oil obtained by SPE had a different appearance with that of obtained by a conventional hydrodistillation method. Indeed, the hydrodistilled oil due to the
there is no thermal degradation of matricin and presence of chamazulene had a blue color while the SPE oil showed a pale yellow color (44). In the SPE oil, there is no thermal degradation of matricin and its conversion to the blue compound chamazulene.

Recently, ninety three compounds have also been identified in the total essential oil of Greek F. communis subsp. communis using a hydrodistillation method. Sesquiterpenes were the most dominant class of compounds in the oil of leaves and inflorescences, while the oil of infructescence was rich in monoterpenes, particularly α-pinene (35.2-40.6%) as the major component (45).

Miscellaneous compounds
Other compounds such as 3,4-methylenedioxy-5-hydroxy-propiophenone (71) (21), phenylpropanoids 1-hydroxy-1-(3'-methoxy- 4',5'-methylenedioxo) phenyl propane (72) and 2-epihel-manticine (73) (21) and elemicin (46) were identified from F. communis (22). An unusual minor component fercooperol (74) which is a cyclic-endoperoxynorlidol derivative has been also reported (47).

Chromones are the other class of compounds which have been isolated from F. communis. For example, an investigation on F. communis grown in turkey caused the identification of two cyclic farnesyl-chromone derivatives (75, 76) (22). The chromone sesquiterpene ferchromone (77) (40) was also obtained from the plant (21).

Acetylenes including ferulinolone [3-(1,2 dihydrofalcarinolonyl)-ferulenol] (18) and decarboxyferulinolone [2-nor-3-(1,2-dihydrofalcicaritinolonyl-ferulenol] (19) are the other class of metabolites identified from the roots of F. communis (48).

Biological effects
Most of in vitro studies on F. communis and its constituents have been focused on their antimicrobial properties. In 1998, Al-Yahya et al, examined anti-bacterial activity of constituents extracted from the rhizome of F. communis (40)
including 14-(O-hydroxycinnamoyloxy)-dauc-4,8-diene (65), the sesquiterpene coumarin ferulenol (1), and the chromane sesquiterpene herchromone (77). The petroleum ether extract of F. communis and its constituents showed anti-bacterial effects. Their findings revealed that the sesquiterpene 14-(O-hydroxycinnamoyloxy)-dauc-4,8-diene possessed strong activity against Staphylococcus aureus, Bacillus subtilis, Streptococcus durans and Enterococcus faecalis comparable to those of streptomycin sulfate. On the other hand, ferulenol exhibited potent activity against four Mycobacterium strains, including M. intracellularure, M. xenopei, M. chelonei and M. smegmatis. The compound 14-(O-hydroxycinnamoyloxy)-dauc-4,8-diene exhibited significant activity against Gram-positive bacteria, while ferchromone was found to be less active (40).

Unasho et al also studied the in vitro antibacterial activities of F. communis root extract against clinical isolates of Streptococcus pyogenes and Streptococcus pneumonia (49). But the fractions of the plant were found to have weak antibacterial effects to the mentioned bacteria.

The antibacterial activities of three daucane sesquiterpenes including acetoxferutinin, oxojaes-keanadiyl anisate (48), ferutidin (22) were examined against Botryotinia fuckeliana, Penicillium digitatum, Penicillium expansum, Monilinia laxa, Monilinia fructigena and Aspergillus spp. F. communis root extract only affected colony growth of Bortryo fuckeliana, Monilinia laxa and Monilinia fructigena and no inhibitory activity was observed on conidial germination under applied experimental concentrations. F. communis aerial part extract showed no activity on colony growth and was not tested on Conidia (31).

Fercoperol (74) which is a cyclic-endoperoxynerolidol derivative has been also reported to have amoebicidal activity. Anti-malarial effects of fercoperol are comparable with other standard anti-malarial compounds (47).

Ferulenol and its acetate exhibited antibacterial activity against Mycobacterium intracellularure, Mycobacterium xenopei, Mycobacterium chelonei and Mycobacterium smegmatis, with MIC values much lower (1.25–5.0 µg/ml) than those of the positive controls streptomycin sulfate, isonicotinic acid hydrazide (INH) and amikacin sulfate (40, 50). In addition, ferulenol showed synergistic action with INH towards the same strains of Mycobacterium.

Plant defensive effects of Ferula extracts have been examined against insect herbivores (such as Spodoptera littoralis and Myzus persicae) and the compounds responsible for these activities were identified (51) by bio-guided fractionation method. The nematicidal (Meliodogyne javanica) and phytotoxic (Lactuca sativa and Lolium perenne) activity of these extracts and compounds have been also investigated (51). Bioassay-guided fractionation led to the identification of ferulenol as the active anti-feedant compound.

Toxicological properties
Consumption of F. communis L. has been found to be associated with bleeding (ferulosis) in animals and humans (52). Studies showed that prenylated 4-hydroxycoumarins play an important role in pro-haemorrhagic effects of F. communis (11, 12, 14, 23, 53).

It has been known for a long time that the consumption of F. communis L. can cause in livestock an often lethal disease known as ferulosis. Cases of human poisoning from ingestion of F. communis have also been reported. Poisoning from F. communis causes symptoms in cattle similar to those described for the intoxication by fermented sweet clover, and it has been suggested that the plant contains antithrombic coumarin derivatives (53-55).

Biological tests established that, among compounds isolated from F. communis, only prenylated coumarins are toxic (56). Ferulenol (20) and ferprenin (24), the prenylated coumarins isolated from toxic variety of giant fennel, exhibited haemorrhagic effects in vivo. Extracts lacking these two compounds still remained toxic to experimental animals. This toxicity was assigned to more polar coumarins which were derivatives of ferulenol and ferprenin (24, 56). Other studies also confirm that only plants containing prenylated coumarins can elicit the toxic symptoms of ferulosis, whereas those containing daucane esters are not toxic (56).

In the root extract of prenylated coumarin-containing plants, based on the ratio of ferulenol to its ō-oxygenated derivatives, two patterns of constituents are detected; one in which ferulenol is the major constituent and one which consists almost exclusively of its more polar ō-oxygenated derivatives (11). But a very similar pattern of constituents is also found in leaves.

The toxic and the non-toxic varieties of F. communis differ not only in the presence of prenylated coumarins or sesquiterpene esters, but also in other classes of metabolites including volatile terpenoids and phenylpropanoids (11).

Alzweiri et al proposed acetylated ferulenol-oxy-ferulenol as a marker for fresh Ferula toxicity by using a metabolomic approach (57). Their results showed that chloroform extract of fresh F. communis had significantly different constituents from those detected in dried plants. One of the main different peaks in HPLC analysis was attributed to the mentioned compound.

Studying the mitochondrial effects of ferulenic acid revealed that it inhibited oxidative phosphorylation (58). Ferulenol has a dual effect on mitochondrial functions depending on concentration. At low concentrations, ferulenol inhibited ATP synthesis, while
it did not have any effect on mitochondrial respiration. In contrast, at higher concentrations, ferulenol inhibited oxygen consumption. This data showed that ferulenol, and *F. communis* chemotype containing ferulenol, might exert their toxicity via other mechanisms including mitochondrial dysfunction (58).

Monti *et al* investigated the mechanisms by which *F. communis* caused severe bleeding and characterized anti-coagulant properties of prenylated coumarin ferulenol (59). Ferulenol did not exert its anti-coagulant activity directly. This compound exhibited hepatocyte cytotoxicity, and at non-cytotoxic concentrations (<100 nM), could reduce factor X biosynthesis. Structure activity studies showed that the presence of the prenyl residue in ferulenol derivatives is essential for ferulenol activity (59). Animals treated with ferulenol indicated a sharp decrease in activity for several coagulation factors (60).

### Cytotoxic and antiproliferative activity

Because of the importance of cytotoxic effects of *F. communis*, we reviewed this activity and its related mechanisms separately in this section. A large number of studies have been performed for the characterization of its cytotoxic compounds. Some investigations suggested that the cytotoxic effect of *F. communis* could be related to ferulenol. For example, Bocca *et al*, investigated cytotoxic activity of ferulenol, and proposed that ferulenol stimulated tubulin polymerization *in vitro*, and inhibited the binding of radiolabeled colchicine to tubulin (61). It rearranged cellular microtubule network into short fibers, and altered nuclear morphology. Remarkably, ferulenol exerted a dose-dependent cytotoxic activity against various human tumor cell lines (61). Determination of the acute LD50 of ferulenol showed that it had a higher LD50 compared to warfarin and thus had a favorable toxicity profile. Hypoprothrombinemia with internal and external hemorrhages caused by the administration of ferulenol in mice was similar to symptoms of ferulosis and anti-vitamin K poisonings. Male mice were more sensitive to intoxication by ferulenol than females (12).

Antiproliferative effects of daucane esters (Figure 5) including certain jaesekanadiol p-hydroxy- and p-methoxybenzoates from *F. communis* on human colon cancer cell lines were investigated (62). Daucane esters from *F. communis* inhibited the growth of WiDr, Colo320-HSR and LS174 colon cancer cells in a dose-dependent manner. LD50 calculated after 72 hr of treatment, revealed that the anti-proliferative capacity of the compounds was in the following descending order: ferutinin (21) > 2α-OH-ferutidin > ferutidin (22) > siol anisate (54) > lapiferin (43) > jaeskeanadiol (68). *Ferula* daucane esters do not act as non-specific toxins randomly impairing the cellular metabolic machinery, but rather act by interaction with specific metabolic pathways (62).

The study on the anti-proliferative mechanism of ferutinin shows that it acts as a calcium ionophore in the T-leukemia cell line Jurkat and this event leads to a collapse of the mitochondrial membrane potential with consequent generation of reactive oxygen species (ROS) that ultimately lead to apoptosis (63).

Dall’Acqua *et al* investigated anti-proliferative activity of constituents from *F. communis* on different cell lines such as HeLa, A549, HL-60, Jurkat, K562, RS
4; 11 and SEM (64). Compounds (1-11, Figure 4) were identified and their anti-proliferative activities have been studied. Compounds (5), (7), and (9) exhibited cytotoxic effects against all the considered cell lines. Compound (7) was the most active against Jurkat while (9) showed the highest activity against all the other tested cell lines. All the most active compounds possessed ring fusion with trans geometry and the 6-(a)-ester linked group (p-methoxybenzoyl or angeloyl), while those with cis geometry (1 and 11) or 4- and 5-epoxy group (2) had poor activity. Also the double bond in the hepta-atomic ring appeared critical (64). The 10-β-hydroxy function or the 10-β-acetox substituent in these compounds is essential for the cytotoxic effects. Notably, for the two isomers (4) and (5) the IC₅₀ is lower or at least the same (for HL-60) in all the cell lines for the compound bearing the 10β-hydroxy group (5). Data suggest that apoptosis may be the major cause of cell death (64).

Dall’Acqua et al, in continuation of their research on anti-proliferative agents from plants, found natural daucane esters isolated from F. communis and Ferulago campestris induced apoptosis in G1 phase in leukemic cells through ROS production (65). Among all isolated compounds, only one of them showed more activity against leukemic cell lines (compound 76). By using structure–activity relationship studies, they realized that there is a relation between cytotoxicity and trans geometry of the ring fusion.

Compound 76 also induces alterations of several intracellular antioxidant enzymes (65). This compound promotes oxidative stress in SEM cells via reducing antioxidant enzymes such as superoxide dismutase and other related enzymes.

**Discussion**

As discussed in previous sections, the most bioactive compounds were highlighted in the mind of readers; however, in this section we have a brief overview on bioactive compounds of giant fennel. Ferulonol (1), a coumarin derivative, is the major constituent of the poisonous chemotype F. communis. Ferulonol was isolated for the first time from F. communis and is the universal precursor of farnesylated 4-hydroxycoumarins (30). As shown in Table 1, ferulonol has diverse pharmacological effects such as antimicrobial, anticoagulant, antifeedant, and antiproliferative activities. Recently, Gliszczynśka et al, have reviewed sesquiterpene coumarins including ferulonol as lead compounds in drug discovery (66).

Ferutinin is a natural phytoestrogen with ionophoretic properties. The beneficial effects of non-poisonous chemotype of F. communis is attributed to phytoestrogens including ferutinin which was isolated for the first time from Ferula tenuisecta Eug. Kor. (67). It has been established that ferutinin has ionomophoretic properties, i.e. it increases the permeability of thymocytes, mitochondria, sarcoplasmic reticulum, liposomes and bilayer lipid membranes (BLM) for cations, especially Ca²⁺ (68). It is more selective for divalent cations versus monovalent cations (69). Ferutinin is typically considered as non-toxic compound that is not able to

**Table 1. Biological activities reported from the bioactive compounds of Ferula communis**

| Compound number | Compound name | Biological activities | Ref. |
|-----------------|---------------|-----------------------|------|
| 57 and other daucane esters | Ferulenol and ω-hydroxyferulenol | Apoptosis inducer through ROS production in leukaemic cells | (56) |
| 1, 65, 77 | Daucone ester 14-(O-hydroxyaminomethoxy) 14,15-diene | Antibacterial activity | (30) |
| 1 | Ferulenol | Pro-haemorrhagic activity | (15) |
| 1, 3 | ω-oxygenated derivatives of ferulenol and ferprenin | Antithrombotic activity | (46) |
| 66 | Fakarindiol | Anti-platelet activity | (79) |
| 1, 65, 77 | Ferulonol, ω-oxygenated derivatives of ferulenol and ferprenin | Anticoagulant activity | (49, 80) |
| 1 | Ferulonol | Antimycobacterial activity, inhibitory activity on succinate ubiquinone reductase, toxic | (40, 52, 81) |
| 21 | Ferutinin, 2α-OH-Ferutidin, Ferutidin | Antiproliferative activity | (53) |
| 21 | Ferulonol | Antibacterial activity | (49, 50) |
| 21 | Ferulonol | Anticoagulant activity | (49, 80) |
| 21 | Ferulonol | Apoptosis inducer | (49, 80) |
| 21 | Ferulonol | Anti-inflammator | (82) |
| 21 | Ferulonol | Antifungal activity, Apoptosis inducer, Anti-cancer, bone formation, Calcium ionophoretic | (54, 59, 63) |
**Table 2. Pharmacological/biological activities reported from *F. communis* in detail**

| Activity       | Dosage form/type of extract | Concentrations/dosages | Tested living system/organ/cell | Active compound(s) | Result(s) | Ref. |
|----------------|-----------------------------|------------------------|---------------------------------|--------------------|-----------|------|
| Antibacterial  | Petroleum ether extract     | 1.25-5.0 mg/ml          | *Staphylococcus aureus*, *Bacillus subtilis*, *Streptococcus durans*, *Enterococcus faecalis*, *Mycobacterium intracellulare*, *Myco. xenopei*, *Myco. Chelonei*, *Myco. Smegmatis* | Ester 14-(0-hydroxycaffeyl-4,8-diene), ferulonol, ferchromone | Ester 14-(0-hydroxycinnamoyloxy)-dauc-4,8-diene exhibited strong activity against *Staph. aureus*, *Bacillus subtilis*, *Strep. durans* and *Entro. faecalis*. Ferulonol showed strong antibacterial activity against *S. aureus*, *B. subtilis*, *S. durans* and *E. faecalis* and four *Mycobacterium* strains. Ferchromone exhibited potent activity against *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus durans*, *Enterococcus faecalis*. | (40) |
| Antibacterial  | 80% methanol crude extracts and hydro alcoholic solvent fractionates | 500 mg/ml to 10000 mg/ml | Clinical isolates of *Strep. pyogenes* and *Strep. pneumoniae* | Acetoxyferutinin, oxojaeskeanadioyl anisate, ferutidin, and ferulonol | Eighty percent ethanol solubilized fraction was found to have antibacterial effects to all assayed bacteria while aqueous solubilized fractions did not exhibit any effect. | (49) |
| Antifungal     | n-hexane                    | ED<sub>50</sub> almost > 400 | The colonies and conidia of *Botryotinia fuckeliana*, *Penicillium digitatum*, *Pen. expansum*, *Monilinia laxa*, *Moni. fructigena* and *Aspergillus* spp | | Root extract presented a fungitoxic effect on the colony growth, but it was not able to inhibit the conidia germination. Aerial part extract showed less activity. | (51) |
| Amoebicidal    |                             |                        |                                 | Fercoperol         |                       |      |
| Antimycobacterial | Petroleum ether            | *Mycobacterium intracellulare*, *M. smegmatis*, *M. xenopei* and *M. chelonei* | Ferulonol | Ferulonol exhibited synergism withisonicotinic acid hydrazide (INH). Its MIC decreased from 5.0 to 0.3 µg/ml. | (40, 50) |
| Anti-coagulant | <100 nM                     | BabyHamster Kidney (BHK) cells | A series of prenylated 4-hydroxycoumarins including ferulonol | They did not directly affect blood coagulation but showed hepatocyte cytotoxicity and, at non-cytotoxic concentrations (<100 nM), impaired factor X biosynthesis (40% reduction). | (59) |
| **Aphid antifeedant** | **Herbivorous insects:** (Spodoptera littoralis and Myzus persicae) **Nematodes:** (Meloidogyne javanica) **Plants:** (Lactuca sativa and Lolium perenne) |
|----------------------|----------------------------------------------------------------------------------------------------------|
| **Aphrodisiac**       | **Male rats** Ferutinin                                                                                     |
| **Aphrodisiac**       | **Ovariectomized rats** Ferutinin                                                                           |
| **Antiproliferative** | **24-46 µg/ml** Ferutinin                                                                                 |
| **Antiproliferative** | **0.8-60 µM** Daucane esters: ferutinin, 2α-hydroxyferutidin, Ferutidin, Siol anisate, Lapiferin, Jaeskeanadiol |
| **Proliferation and osteoblastic differentiation** | **10-8 and 10 - 9 M** Ferutinin                                                                           |
exert anticoagulant activities like prenylated coumarins. Ferutinin, unlike the other Ca²⁺-ionophores which most likely increases (Ca²⁺) via the activation of platelet plasma membrane Ca²⁺ channels and the release of Ca²⁺ from intracellular stores, increases Ca²⁺ levels because of its Ca²⁺-ionophoretic properties, and does not induce blood platelet aggregation. Ferutinin stimulates the expression of the active form of the GP Ib-Ⅸa complex and whole blood platelet aggregation only weakly and has no statistically significant effect on the binding of fibrinogen. In fact, ferutinin has inconsistent effects; it raises intra-platelet Ca²⁺ concentration but fails to have an effect on spontaneous blood platelet aggregation. This pattern of responses may be caused by the combination of ferutinin-related Ca²⁺ ionophoric effect and estrogenic properties (70).

Anti-proliferative, cytotoxic and apoptotic effects of ferutinin in different cell lines have been also investigated (62, 71-73). This compound induces calcium mobilization from external and internal stores and eventually triggers apoptosis through a caspase-3 dependent pathway. It caused morphological changes, DNA damage, significant regression in tumor size in cancerous cells, while it showed less toxic effects in non-tumoral cells (74). According to structure-activity studies, (p-hydroxylation) of the benzoyl moiety is crucial for the activity (71, 75) while the parent polyol (jaeschkeanadiol, 2a) was inactive. Homologation, vinylation, methylation of the p-hydroxy substituent and the introduction of oxygen functions on the adjacent carbons were essential for its activity (75).

Studying the effect of ferutinin on human red blood cells revealed that it induced in vitro apoptosis through membrane permeabilization and calcium influx (76). Death promoting activities of ferutinin in a number of cancer cells by opening the mitochondrial permeability transition pores have been documented well. The induction of apoptosis in human red blood cells is known as eryptosis or erythroptosis. Ferutinin causes eryptosis/erythroptosis in human red blood cells and simultaneously increases caspase-3 activity and the cytosolic free Ca²⁺ ion level (76).

Phytoestrogens as alternative drugs can be used for the treatment of osteoporosis and many studies have been investigated the anti-osteoporosis effects of phytoestrogens (77). Since ferutinin has estrogenic activity, its beneficial effect on osteoporosis has been investigated. For instance, oral administration of ferutinin in recovering severe osteoporosis has been studied in ovariectomized rats (78, 79). It could increase the recovery of bone loss caused by severe estrogen deficiency. Thus ferutinin can be listed among the potential compounds for the treatment of postmenopausal osteoporosis. Expression of the osteoblast phenotype markers osteocalcin (OCN), osteopontin (OPN), collagen I, RUNX-2 and osterix (OSX), increase in calcium deposition and osteocalcin secretion are proposed mechanisms for this activity of ferutinin (80). Anti-inflammatory (81), antibacterial (82, 83), aphrodisiac (84-86) and fungicidal (87) properties are other activities proposed for this compound.

Concluding remarks

F. communis subsp. communis, namely, giant fennel, showed versatile biological activities (Table 2) with various bioactive natural products. Two chemotypes of F. communis L. have been characterized with different chemical constituents. The toxic chemotype mainly produces prenylated coumarins such as ferulenol (1) that are responsible for a lethal haemorrhagic disorder called ferulosis. The non-toxic chemotype contains daucane type sesquiterpenoids such as ferutinin (21) and its pharmacological activities are attributed to these compounds. Antibacterial and cytotoxic activities are two areas that have been covered in previous studies. However, further studies should be focused on mechanisms behind the antibacterial and cytotoxic activities, and those biological activities that have been reported traditionally.

References

1. Iranshahi M, Amin GR, Jalalizadeh H, Shafiee A. New germacrane derivative from Ferula persica Willd. var. latisecta Chamberlin. Pharm Biol 2003; 41:431-433.
2. Iranshahi M, Ghiadi M, Sahebkar A, Rahimi A, Bassarello C, Piacente S, et al. Badrakemonin, a new eremophilane-type sesquiterpene from the roots of Ferula badrakema Kos.-Pol. Iran J Pharm Res 2009; 8:275-279.
3. Iranshahi M, Rezaee R, Sahebkar A, Bassarello C, Piacente S, Pizza C. Sesquiterpene coumarins from the fruits of Ferula badrakema. Pharm Biol 2009; 47:344-347.
4. Iranshahi M, Kalateghi F, Sahebkar A, Sardashi A, Schneider B. New sesquiterpene coumarins from the roots Ferula flabelliflora. Pharm Biol 2010; 48:217-220.
5. Iranshahi M, Masullo M, Asili A, Hamedzadeh A, Jahanbin B, Festa M, et al. Sesquiterpene coumarins from Ferula gummosa. J Nat Prod 2010; 73:1950-1962.
6. Kasian J, Iranshahy M, Masullo M, Piacente S, Ebrahimi F, Iranshahi M. Sesquiterpene lactones from Ferula oopoda and their cytotoxic properties. J Asian Nat Prod Res 2014; 16:248-253.
7. Iranshahi M, Amin G, Amini M, Shafiee A. Sulfur containing derivatives from Ferula persica var. latisecta. Phytochemistry 2003; 63:965-966.
8. Iranshahi M, Amin G, Salehi Soroush MH, Shafiee A, Hadjiaahloua N. Sulphur containing compounds in the essential oil of Ferula persica Willd. var. persica. Flavour Frag J 2006; 21:260-261.
9. Iranshahi M, Hassanzadeh-Khayyat MH, Fazly Bazzaz BS, Sabet Z, Enayati F. High content of polysulfides in the volatile oil of Ferula latisecta Rech. F et Aell. fruits and antimicrobial activity of the oil. J Essent Oil Res 2008; 20:183-185.
10. Iranshahi M. A review of volatile sulfur-containing compounds from terrestrial plants: biosynthesis,
distribution and analytical methods. J Essent Oil Res 2012; 24:393-434.
11. Appendino G, Tagliapietra S, Gariboldi P, Mario Nano G, Picci V. δ-Oxygenated prenylated coumarins from Ferula communis. Phytochemistry 1988; 27:3619-3624.
12. Fraigoi O, Lamnaouer D, Faouzi MYA. Acute toxicity of ferulenol, a 4-hydroxycoumarin isolated from Ferula communis L. Vet Hum Toxicol 2002; 44:5-7.
13. Amoldi L, Ballero M, Fuzziati N, Maxia A, Mercalli E, Pagni L. HPLC-DAD-MS identification of bioactive secondary metabolites from Ferula communis roots. Fitoterapia 2004; 75:342-354.
14. Appendino G, Cravotto G, Sterner O, Ballero M. Oxygenated sesquiterpenoids from a nonpoisonous sardinian chemotype of giant fennel (Ferula communis). J Nat Prod 2001; 64:393-395.
15. Gunther RT. The Greek Herbal of Dioscorides. New York: Hafner; 1959.
16. Heywood VH. The Biology and Chemistry of the Umbelliferae. London: Academic Press; 1972.p.1247-1249.
17. Collelente S. An Illustrated Guide to the Flowers of Saudi Arabia. London: Academic Press; 1985.
18. Bnouham M, Melighi H, Legguy A, Ziyat A. Medicinal plants used in the treatment of diabetes in Morocco. Int J Diabet Metabol 2002; 10:33-50.
19. Dioscorides. DE MATERIA MEDICA. South Africa: AIBIDIS PRESS; 2000p. 468.
20. Valle MG, Appendino G, Nano GM, Picci V. Prenylated coumarins and sesquiterpenoids from Ferula communis. Phytochemistry 1986; 26:253-256.
21. Miski M, Mabry TJ. Daucane esters from Ferula communis subsp. communis. Phytochemistry 1985; 24:1735-1741.
22. Miski M, Jakupovic J. Cyclic farnesyl-coumarin and farnesyl-cholesterol derivatives from Ferula communis subsp. communis. Phytochemistry 1990; 29:1995-1998.
23. Valle MG, Appendino G, Nano GM, Picci V. Prenylated coumarins and sesquiterpenoids from Ferula communis. Phytochemistry 1986; 26:253-256.
24. Appendino G, Tagliapietra S, Nano GM, Picci V. Ferprenin, a prenylated coumarin from Ferula communis. Phytochemistry 1988; 27:944-946.
25. Lamnaouer D, Bodo B, Martin MT, Molho D. Ferulenol and ω-hydroxyferulenol, toxic coumarins from Ferula communis var. genuina. Phytochemistry 1987; 26:1613-1615.
26. Appendino G, Tagliapietra S, Paglio L, Nano GM, Monti D, Picci V. Sesquiterpenoid esters from the roots of Ferula communis. Phytochemistry 1990; 29:1481-1484.
27. Abd El-Razek MH, Ohta S, Hirata T. Terpenoid coumarins of the genus Ferula. Heterocycles 2003; 60:689-716.
28. Iranshahi M, Amanalahi F, Schneider B. New sesquiterpene coumarin from the roots of Ferula latissima. Avicenna J Phytomed 2012; 2:133-138.
29. Nazari ZE, Iranshahi M. Biologically active sesquiterpene coumarins from Ferula species. Phytother Res 2011; 25:315-323.
30. Carboni S, Malaguzzi V, Marsili A. Ferulenol a new coumarin derivative from Ferula communis. Tetrahedron Lett 1964; 5:2783-2786.
31. Mamoci E, GvozdI, Simeone V, Mondelli D, Al-Bitar L, Caboni P. Chemical composition and in vitro activity of plant extracts from Ferula communis and Ditrichia viscosa against postharvest fungi. Molecules 2011; 16:2609-2625.
32. Lamnaouer D, Fraigoi O, Martin MT, Gallard JF, Bodo B. Structure of isoferprenin, a 4-hydroxycoumarin derivative from Ferula communis var. genuina. J Nat Prod 1991; 54:576-578.
33. Appendino G, Tagliapietra S, Cravotto G, Nano GM. Structure and synthesis of a prenylated acetophene from Ferula communis. Gaz Chem Ital 1989; 119:385±388.
34. Pinar M, Rodríguez B. A new coumarin from Ferula lasiosii and the correct structure of coladinin. Phytochemistry 1977; 16:1987-1989.
35. Abu-Gabal NS, Edris FM, Abu Mustafa EA. Further investigation on Ferula communis grown in Saudi Arabia. Egypt J Chem 2008; 51:107-114.
36. Iranshahi M, Amin G, Shafiee A. A New Coumarin from Ferula persica. Pharm Biol 2004; 42:440-442.
37. Iranshahi M, Shahverdi AR, Mirjani R, Amin G, Shafiee A. Umbelliprenin from Ferula persica roots inhibits the red pigment production in Serratia marcescens. Z Naturforsch C 2004; 59:506-508.
38. Miski M, Mabry TJ. Fercocolide, a type of sesquiterpene lactone from Ferula communis subsp. communis and the correct structure of vaginatin. Phytochemistry 1986; 25:1673-1675.
39. Lamnaouer D, Martin MT, Molho D, Bodo B. Isolation of daucane esters from Ferula communis var. brevifolia. Phytochemistry 1989; 28:2711-2716.
40. Al-Yahya MA, Muhammad I, Mirza HH, El-Ferayl FS. Antibacterial constituents from the rhizomes of Ferula communis. Phytother Res 1990; 12:335-339.
41. Sahebkar A, Iranshahi M. Volatile constituents of the genus Ferula (Apiaceae): A review. J Essent Oil Bear Pl 2011; 14:504-531.
42. Sahebkar A, Iranshahi M. Biological activities of essential oils from the genus Ferula (Apiaceae). Asian Biomed 2010; 4:835-847.
43. Ferrari B, Toni F, Casanova J. Composition and chemical variability of Ferula communis essential oil from Corsica. Flavour Frag J 2005; 20:180-185.
44. Marongiu B, Piras A, Porcedda S. Comparative analysis of the oil and supercritical CO2 extract of Ferula communis L. J Essent Oil Res 2005; 17:150-152.
45. Manolakou S, Tsakou O, Yannitsaros A. Volatile constituents of Ferula communis L. subsp. communis growing spontaneously in Greece. Record Nat Prod 2013; 7:54-58.
46. Maggi F, Lucarini D, Tirillini B, Sagratini G, Papa F, Vittori S. Chemical analysis of the essential oil of Ferula glauca L. (Apiaceae) growing in Marche (central Italy). Biochem Syst Ecol 2009; 37:432-441.
47. Miski M, Mabry TJ, Bohlmann F. Fercoperol, an unusual cyclic-endoperoxynoriodol derivative from Ferula communis subsp. communis. J Nat Prod 1986; 49:916-918.
48. De Pascual Teresa J, Villaseca MA, Hernandez JM. Complex acetylens from the roots of Ferula communis. Planta Med 1986; 6:458-462.
49. Unasho A, Geyid A, Melaku A, Debela A, Mekasha A, Girma S, et al. Investigation of antibacterial activities of Albizia gummifera and Ferula communis on Streptococcus pneumoniae and Streptococcus pyogenes. Ethiop Med J 2009; 47:25-32.
50. Mossa JS, El-Feraily FS, Muhammad I. Antimicrobial bacterial constituents from Juniperus procera, Ferula communis and Plumbago zeylanica and their in vitro synergistic activity with icositonic acid hydrazide. Phytother Res 2004; 18:934-937.

51. Mamoci E, Cavoski I, Andres MF, Diaz CE, Gonzalez-Coloma A. Chemical characterization of the aphid antifeedant extracts from Dittrichia viscosa and Ferula communis. Biochem Syst Ecol 2012; 43:101-107.

52. Bruneton J. Toxie plants dangerous to human and animals. Paris: Lavoiser publishing Inc; 1999.

53. Rubiolo P, Matteodo M, Riccio G, Ballero M, Christen P, Fleury-Souverain S, et al. Analytical discrimination of poisonous and nonpoisonous chemotypes of giant fennel (Ferula communis L.) through their biologically active and volatile fractions. J Agric Food Chem 2006; 54:7556-7563.

54. Carta A. Ferulosis; isolation of the substance with hypoprothrombinemizing action from the galbanum of fennel (Ferula communis). Boll Soc Ital Biol Sper 1951; 27:690-693.

55. Lammauer D. Anticoagulant activity of coumarins from Ferula communis L. Therapie 1999; 54:747-751.

56. Tugliapietra S, Aragoni M, Ugazio G, Nano GM. Experimental studies on the toxicity of some compounds isolated from Ferula communis in the rat. Res Commun Chem Pathol Pharmacol 1989; 66:333-336.

57. Alzweiri M, Al-Shudeifat M, Al-Khalidi K, Al-Hiari Y, Alfi F. Acetylated feruleral-oxy-feruleral as a proposed marker for fresh Ferula toxicity: A metabolomic approach. J Liq Chromatogr Relat Technol 2015; 38:283-298.

58. Lahouel M, Zini R, Zellagui A, Rhouati S, Carrupt P-A, Morin D. Feruleral specifically inhibits succinate ubiquinone reductase at the level of the ubiquinone cycle. Biochem Biophys Res Commun 2007; 355:252-257.

59. Monti M, Pinotti M, Appendino G, Dall’Acqua S, Dittrichia zeylanica and their in vitro synergistic activity with icositonic acid hydrazide. Phytother Res 2004; 18:934-937.

60. Tugliapietra S, Aragoni M, Ugazio G, Nano GM. Experimental studies on the toxicity of some compounds isolated from Ferula communis in the rat. Res Commun Chem Pathol Pharmacol 1989; 66:333-336.

61. Monti M, Pinotti M, Appendino G, Dall’Acqua S, Dittrichia zeylanica and their in vitro synergistic activity with icositonic acid hydrazide. Phytother Res 2004; 18:934-937.

62. Poli F, Appendino G, Sacchetti G, Ballero M, Maggiano N, Ranelletti FO. Antiproliferative effects of daunecus esters from Ferula communis and F. arragoni on human colon cancer cells lines. Phytother Res 2005; 19:152-157.

63. Macho A, Blanco-Molina M, Spagliardi P, Appendino G, Bremner P, Heinrich M, et al. Calcium ionophoretic and apoptotic effects of ferutinin in the human Jurkat T-cell line. Biochem Pharmacol 2004; 68:875-883.

64. Dall’Acqua S, Linardi MA, Maggi F, Nicoletti M, Petitto V, Innocenti G, et al. Natural daunecus sesquiterpenes with antiproliferative and proapoptotic activity against human tumor cells. Bioorg Med Chem 2011; 19:5876-5885.

65. Dall’Acqua S, Linardi MA, Bortolozzi R, Glauser M, Marzocchini S, Maggi F, et al. Natural daunecus esters induces apoptosis in leukemic cells through ROS production. Phytochemistry 2014; 108:147-156.

66. Gliszczyńska ABrodieus PE. Sesquiterpenes coumarins. Phytochem Rev 2012; 11:77-96.

67. Saidkhodzhaev AI, Nikonorov GK. The structure of ferutinin. Chem Nat Prod 1975; 9:25-26.

68. Zamaras MV, Hagelians AI, Abramov AY, Ternovsky VI, Merzlyak PG, Tashmukhamedova BA, et al. Calcium ionophoretic properties of ferutinin. Cell Calcium 1997; 22:235-241.

69. Abramov AY, Zamaras MV, Hagelians AI, Azimov RR. Krasilnikov OV. Influence of plant terpenoids on the permeability of mitochondria and lipid bilayers. Biochim Biophys Acta 2001; 1512:98-110.

70. Zamaras MV, Charishnikova O, Saidkhodjaev A, Isidorov V, Granosik M, Rozalski E, et al. Calcium mobilization by the plant estrogen ferutinin does not induce blood platelet aggregation. Pharmacol Rep 2010; 62:1117-1126.

71. Macho A, Blanco-Molina M, Spagliardi P, Appendino G, Bremner P, Heinrich M, et al. Calcium ionophoretic and apoptotic effects of ferutinin in the human Jurkat T-cell line. Biochem Pharmacol 2004; 68:875-883.

72. Makin MM, Nakhaeizadeh H, Bahrami AR, Iranshahi M, Arghiani R, Sassouli FB. Ferutinin, an apoptosis inducing terpenoid from Ferula ovina. Asian Pac J Cancer Prev 2014; 15:2123-2128.

73. Ferretti M, Cavani F, Manni P, Carnevalge V, Bertoni L, Zavatti M, et al. Ferutinin dose-dependent effects on uterus and mammary gland in ovariectomized rats. Histol Histopathol 2014; 29:1027-1037.

74. Arghiani N, Matin MM, Bahrami AR, Iranshahi M, Sazgarnia A, Sassouli FB. Investigating anticancer properties of the sesquiterpene ferutinin on colon carcinoma cells, in vitro and in vivo. Life Sci 2014; 109:87-94.

75. Appendino G, Spagliardi P, Cravotto G, Pocock V, Milligan S. Daucane Phytoestrogens: A Structure–Activity Study. J Nat Prod 2002; 65:1612-1615.

76. Gao M, Wong SY, Lau PM, Kong SK. Ferutinin induces in vitro erythropoiesis/erythroptosis in human erythrocytes through membrane permeabilization and calcium influx. Chem Res Toxicol 2013; 26:1218-1228.

77. Fu SW, Zeng GF, Zong SH, Zhang ZY, Zhou B, Fang Y, et al. Systematic review and meta-analysis of the bone protective effect of phytoestrogens on osteoporosis in ovariectomized rats. Nutr Res 2014; 34:467-477.

78. Ferretti M, Bertoni L, Cavani F, Zavatti M, Recsa E, Carnevalge V, et al. Influence of ferutinin on bone metabolism in ovariectomized rats: II. Role in recovering osteoporosis. J Anat 2010; 217:48-56.

79. Cavani F, Ferretti M, Carnevalge V, Bertoni L, Zavatti M, Palumbo C. Effects of different doses of ferutinin on bone formation/resorption in ovariectomized rats. J Bone Miner Metab 2012; 30:619-629.

80. Zavatti M, Recsa E, Bertoni L, Maraldi T, Guida M, Carnevalge V, et al. Ferutinin promotes proliferation and osteoblastic differentiation in human amniotic fluid and dental pulp stem cells. Life Sci 2013; 92:993-1003.

81. Geroushi A, Auzi AA, Elhawi AS, Elzawam F, Elsherif A, Nahar L, et al. Anti-inflammatory effects
sesquiterpenes from the root oil of Ferula hermonis. Phytother Res 2011; 25:774-777.
82. Abourashed EA, Galal AM, Slibi AM. Antimycobacterial activity of ferutinin alone and in combination with antitubercular drugs against a rapidly growing surrogate of Mycobacterium tuberculosis. Nat Prod Res 2011; 25:1142-1149.
83. Al-ja'Fari AH, Vila R, Freixa B, Costa J, Cañigueral S. Antifungal compounds from the rhizome and roots of Ferula hermonis. Phytother Res 2013; 27:911-915.
84. Zanoli P, Rivasi M, Zavatti M, Brusiani F, Vezzalini F, Baraldi M. Activity of single components of Ferula hermonis on male rat sexual behavior. Int J Impot Res 2005; 17:513-518.
85. Zavatti M, Montanari C, Zanoli P. Role of ferutinin in the impairment of female sexual function induced by Ferula hermonis. Physiol Behav 2006; 89:656-661.
86. Zanoli P, Zavatti M, Geminiani E, Corsi L, Baraldi M. The phytoestrogen ferutinin affects female sexual behavior modulating ERα expression in the hypothalamus. Behav Brain Res 2009; 199:283-287.
87. Al-Mughrabi KL, Aburjai TA. Fungitoxic activity of root extracts from Ferula harmonis. Phytopathol Mediterr 2003; 42:141-148.
88. Appendino G, Tagliapietra S, Nano GM, Picci V. An anti-platelet acetylene from the leaves of Ferula communis. Fitoterapia 1993; 64:179.
89. Lamnaouer D. Anticoagulant activity of the coumarins of Ferula communis L. Activité anticoagulante des coumarines de Ferula communis L. Therapie 1999; 54:747-751.
90. Appendino G, Mercalli E, Fuzzati N, Arnoldi L, Stavri M, Gibbons S, et al. Antimycobacterial coumarins from the Sardinian giant fennel (Ferula communis). J Nat Prod 2004; 67:2108-2110.
91. Lahouel M, Zini R, Zellagui A, Rhouati S, Carrupt PA, Morin D. Ferulenol specifically inhibits succinate ubiquinone reductase at the level of the ubiquinone cycle. Biochem Biophys Res Commun 2007; 355:252-257.