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Pharmacological Activities and Chemical Constituents of *Ferula szowitsiana* DC

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Ferula is a genus of endemic plants in Mediterranean area and central Asia which many species have been traditionally used in folk medicine. *Ferula szowitsiana* is one of the ethnomedicinal plants in the genus that is mostly used in Azerbaijan and neighbouring countries such as Iran, Turkey and Afghanistan. Many scientific studies have been carried out and a wide range of pharmacological effects of the plant have been reported, including anti-cancer, anti-oxidant, anti-inflammation to anti-microbial and anti-biotic modulation activities. Notably, more than 200 compounds consisting of essential oils, coumarins, phenylpropanoid derivative and steroidal compounds have been identified from different parts of the plant and have been evaluated for a variety of biological activities. Despite this, a comprehensive review for this plant is still lacking. The aim of this review is to cover and summarize the biological activities of the active compounds derived from *F. szowitsiana*.

Key words: *Ferula szowitsiana*, chemical constituents, biological activities

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INTRODUCTION

Ferula (means "rod" in Latin) is a genus of about 170 different species that belongs to the Umbelliferae (Apiaceae) family. The plants grow mostly in arid climate such as the Mediterranean area and central Asia. *Ferula* species are 1-4 m tall herbaceous plants, with tripinnate leaves and yellow flowers on large umbels. Many species of this genus are used to produce essential oils or aromatic resins which have unique therapeutic values in traditional medicine (Chen *et al*., 2000). Around 15 species are indigenous in Iran and the Persian name for most of these species is known as "Koma" (Mozaffarian, 1966, 1983).

The chemical constituents derived from *Ferula* sp. (aerial parts and roots) have been extensively investigated by a few research groups (Diab *et al*., 2001; Iranshahi *et al*., 2004a; Abd El-Razek *et al*., 2003). Phytochemical studies revealed that the plant is a potential source of sesquiterpene derivatives especially sesquiterpene coumarins (Shahverdi *et al*., 2006; Iranshahi *et al*., 2004b, 2007a, b, 2008; Ahmed, 1999; Abd El-Razek *et al*., 2001) humulanes, daucanes, guainanes, germacranes, eudesmanes and himachalanes (Gonzalez and Barrera, 1995; Appendino *et al*., 1997; Kojima *et al*., 1999; Su *et al*., 2000a, b).

Ferula szowitsiana DC is an ethnomedicinal plant found in Iran, Turkey and Afghanistan. This plant is widely used as anti-helminthics and anti-septic in traditional medicine of these countries. A vast variety of biological activities and pharmacological effects of the extracts or pure compounds isolated from *F. szowitsiana* have been reported by many investigators, including anti-cancer (Barthomeuf *et al*., 2008; Hanafi-Bojd *et al*., 2011; Soltanzad *et al*., 2012), anti-oxidant (Soltani *et al*., 2010), anti-genotoxicity (Gooshchi *et al*., 2012), anti-inflammation (Kohno *et al*., 2011), anti-microbial (Iranshahi *et al*., 2007a; Ozek *et al*., 2008) and antibiotic activities (Shahverdi *et al*., 2007; Bazzazz *et al*., 2009; Bazzaz *et al*., 2010) (Fig. 1). In this review, we will discuss about the chemical contents and the medicinal properties of *F. szowitsiana*.

Chemical Constituents of *F. szowitsiana* DC: Over the years, many groups have isolated an array of bioactive compounds from different species of *Ferula*. The plant is known to be rich in coumarins, particularly sesquiterpene coumarins (Abd El-Razek *et al*., 2003). The phytochemical investigations of *F. szowitsiana* DC have resulted in isolation and identification of various types of compounds including monoterpene coumarins, sesquiterpene coumarins, phenylpropanoid derivatives and steroidal compounds (Table 1). The isolation of the compounds was obtained by column chromatographic techniques while identification of compounds was done by spectroscopic methods including ^{1}H and ^{13}C-NMR, mass experiments. Essential oils of the aerial, leaves and stems of *F. szowitsiana* DC were also extracted by hydrodistillation and analyzed by GC and GC/MS methods.

Anti-cancer property: Malignant melanoma is the most common form of fatal skin cancer and the eighth most

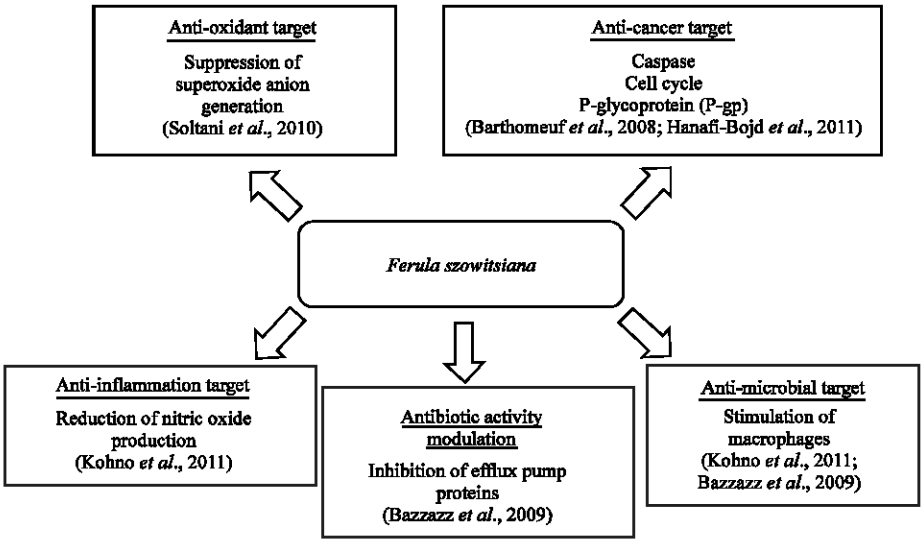

Fig. 1: Overview of biological effects and targeted signaling pathways by *F. szwotsiana*

Table 1: Essential oils and compounds isolated from *F. szowitsiana*

Compounds	Parts	Isolated by	Compounds	Parts	Isolated by
Umbelliferon-7-apiosyl (16) glucoside	Roots	Gooshchi *et al.* (2012)	αterpinene		
Ñ-hydroxy phenylethanoid glucoside			Heptanal		
Galbanic acid			dehydro-1,8-cineole		
Umbelliferon β-D [6′ (ferolyle)-glucoside]			Limonene		
Umbelliferon			1,8-cineole		
Essential oil	Aerial	Habibi *et al.* (2006)	β-phellandrene		
α-pinene			(Z)-3-hexenal		
Germacrene D			2-pentylfuran		
β-pinene			(Z)-β-ocimene		
Epi-α-cadinol			γ-terpinene		
Myrcene			(E)-β-ocimene		
Bicyclogermacrene			P-cymene		
β-phellandrene			Terpinolene		
Sabinene			Octanal		
(E)-β-ocimene			Tridecane		
α-copaene			2-hexylfuran		
β-cubebene			6-methyl-5-hepten-2-one		
β- elemene			Hexyl isobutyrate		
β-caryophyllene			Hexanol		
γ-elemene			α-pinene oxide		
α -humulene			(Z)-3-hexenol		
δ-cadinene			Nonanal		
(E)-γ-bisabolene			Rose furan		
Occidentalol			1-octen-2-one		
Germacrene B			Hexyl 2-methylbutyrate		
Spathulenol			α-campholene aldehyde		
β-copaene-4 -ol			2,5-dimethylstyrene		
1-epi-cubenol			1-octen-3-ol		
Epi-α-cadinol			Hexyl isovalerate		
α-muurolol			Heptanol		
Sesquiterpene coumarins	Roots	Iranshahi *et al.* (2007a)	α-cubebene		
Szowitsiacoumarin A			Trans-sabinene hydrate		
Szowitsiacoumarin B			4,8-epoxyterpinolene		
Auraptene			Longipinene		
Umbelliprenin			Octyl acetate		
Galbanic acid			α-ylangene		
Methyl galbanate			α-copaene		
Farnesiferol B			α-campholene aldehyde		
Farnesiferol C			Decanal		
Persicasulfide A			(E,E)-2,4-heptadienal		
Phenylpropanoid derivative			α-bourbonene		
2-epihelmanticine			β-bourbonene		
Steroidal compounds			Camphor		
β-sitosterol			Benzaldehyde		
Stigmasterol			Dihydroachillene		
Coumarins		Kohno *et al.* (2011)	(E)-2-nonenal		
Farnesiferol A			Linalool		
Badrakemone			Cis-sabinene hydrate		
Umbelliprenin			Octanol		
Aurapten			Trans-p-menth-2-en-1-ol		
Methyl galbanate			a-bergamotene		
Galbanic acid			aristolene		
Galbanic Acid	Roots	Hanafi-Bojd *et al.* (2011)	β-ylangene		
Galbanic Acid		Bazzaz *et al.* (2010)	Pinocarvone		
Auraptene	Roots	Soltani *et al.* (2010)	Bornyl acetate		
Tricyclene	Leaves and stem	Ozek *et al.* (2008)	Trans-β-bergamotene		
α-pinene			β-elemene		
α-thujene			β-copaene		
Camphene			Calarene (b-gurjunene)		
Hexanal			Terpinen-4-ol		
Undecane			β-caryophyllene		
β-pinene			Guaia-6,9-diene		
Sabinene			Myrtenal		
Thuja-2,4(10)-diene			γ-elemene		
δ-3-carene			Octyl 3-methylbutyrate (octyl isovalerate)		
Myrcene			(E)-2-decenal		
p-mentha-1,7(8)-diene (pseudolimonene)			Cis-verbenol		

Table 1: Continue

Compounds	Parts	Isolated by	Compounds	Parts	Isolated by
Trans-pinocarveol			1,5-epoxy-salvial(4)14-ene		
Sesquisabinene B			Cubebol		
(Z)-β-farnesene			(E)-b-ionone		
α-humulene			Dodecanol		
Trans-verbenol			γ-calacorene		
Selina-4,11-diene (=4,11-eudesmadiene)			Isocaryophyllene oxide		
(E)-β-farnesene			Caryophyllene oxide		
p-mentha-1,8-dien-4-ol (= limonen-4-ol)			Salvial-4(14)-en-1-one		
Myrtenyl acetate			Humulene epoxide-I		
γ-muurolene			(E)-nerolidol		
α-terpineol			Humulene epoxide-II		
Guaioxide			Humulene epoxide-III		
Borneol			1-epi-cubenol		
Dodecanal			Elemol		
Verbenone			Guaiol		
Germacrene D			10-epi-γ-eudesmol		
Zingiberene			Hexahydrofarnesyl acetone		
δ-guaiene (= ?bulnesene)			Rosifoliol		
β-bisabolene			Spathulenol		
α-selinene			γ-eudesmol		
Cis-piperitol t -			Eremoligenol		
γ-bisabolene			T-muurolol		
δ-cadinene			α-guaiol		
γ-cadinene			α-bisabolol		
β-sesquiphellandrene			Bulnesol		
Kessane			α-eudesmol		
Ar-curcumene			β-eudesmol		
Selina-3,7(11)-diene			Alismol (guaia-6,10(4)-dien-4 -ol)		
Myrtenol			Myristicin		
Nerol			Tricosane		
(E)-2-decenol			Caryophylla-2(12),6(13)-dien-5 -ol (caryophylladienol I)		
β-damascone			Caryophylla-2(12),6-dien-5 -ol(caryophyllenol I)		
(E)-β-damascenone			Eudesma-4(15),7-dien-1 -ol		
2,6-dimethyl-3(E),5(E),7-octatriene-2-ol			10-hydroxycalamenene		
(E)-anethole			Caryophylla-2(12),6-dien-5 -ol (caryophyllenol II)		
Cuparene			Aristolone		
Geraniol			Pentacosane		
p-cymen-8-ol			Apiole		
(E)-geranyl acetone			Dodecanoic acid		
Undecanol			Phytol		
geranyl isovalerate			Heptacosane		
1,5-epoxy-1(10)-cadinene			Tetradecanoic acid (myristic acid)		
Epi-cubebol			Epoxy-trans-pseudoisoeugenyl angelate		
Tetradecanal			Hexadecanoic acid (palmitic acid)		
α-calacorene					

common cancer in the United States (Parker *et al*., 1996; Landis *et al*., 1999). Its incidence among Caucasian population is in a rise in the past 20 years (Rigel *et al*., 1996; Greenlee *et al*., 2001). Barthomeuf *et al*. (2008) studied the anti-cancer property of *F. szowitsiana* on malignant melanoma. They reported high inhibitory activity of umbelliprenin isolated from *F. szowitsiana* roots against human M4Beu metastatic pigmented malignant melanoma cell line. They purified umbelliprenin ($C_{24}H_{30}O_3$, MW: 366) and auraptene ($C_{19}H_{22}O_3$, MW: 298.4) to test against a number of melanoma cells using Resazurin Reduction Test (RRT). Umbelliprenin (IC_{50} = 12.4±0.5 μM) significantly inhibited the growth of M4Beu cells at a lower dose, compared to auraptene (IC_{50} = 17.2±0.7 μM) and the standard drug, cisplatin (IC_{50} = 23.1±0.8 μM). They also showed the ability of umbelliprenin to reduce the serum-induced proliferation of M4Beu at 25 mM through cell cycle blockade in G1 and induction of dose-dependent apoptosis (Barthomeuf *et al*., 2008).

In addition to M4Beu, they tested the activity of umbelliprenin and auraptene in human primary fibroblasts to evaluate the selectivity index of the compounds and also in other cancer cells including PA1 (ovary teratocarcinoma), MCF7 (breast adenocarcinoma), PC3 (androgen-resistant prostate carcinoma), DLD1 (colon adenocarcinoma) and A549 (non-small cell lung carcinoma). Both compounds exhibited high inhibitory activity against all carcinoma cell lines. At concentration of 25 mM, minimal cytotoxic effect of umbelliprenin was observed in primary fibroblasts, suggesting its significant selectivity between normal

and malignant cells. However, some cytostatic effects were observed at that concentration (Barthomeuf *et al*., 2008).

Multi-Drug Resistance (MDR) is a phenomenon of tumor cells exhibiting resistance to different anti-cancer drugs (Liscovitch and Lavie, 2002). One of the major cellular mechanisms that mediate MDR is the over-expression of a 170 kDa plasma membrane protein, named ABCB1 or P-gp (Ambudkar *et al*., 1999). In the study by Hanafi-Bojd *et al*. (2011), P-gp-over-expressing cell line MCF7/Adr was used to evaluate the inhibitory activity of galbanic acid isolated from *F. szowitsiana* roots and farnesiferol A isolated from *F. Persica* roots, against P-gp for two exposure times (15 and 30 min). Galbanic acid exhibited high potential to serve as a proper MDR inverting candidate, due to its significant inhibitory effect for both exposure times (Hanafi-Bojd *et al*., 2011). Meanwhile, farnesiferol A at 0.5 μg mL^{-1} inhibits P-gp transporter at 15 min after treatment. At this exposure time, it demonstrated higher activity compared to standard drug, verapamil. Of note, Farnesiferol A has been successfully isolated from *F. szowitsiana* (Kohno *et al*., 2011).

Cytotoxicity and anti-cancer activity of methanolic fraction of *F. szowitsiana* was also examined on lung cancer (Soltanzad *et al*., 2012). Lung cancer is the most frequent cancer in the world, which ranked as the major cause of world-wide cancer death (Haugen, 2008; Skarda *et al*., 2008). Malignant lung cancer may spread into nearby tissue and other parts of the body through metastasis. The major difficulty faced in treating lung cancer is the resistance of lung cancer to chemotherapeutic drugs. Thus, discovery of novel drug with new targets will ease drug resistance problem in lung cancer (Shanker *et al*., 2010).

Soltanzad *et al*. (2012) showed that the *F. szowitsiana* methanolic extract inhibited the proliferation of A549 cells in a dose-dependent manner using MTT assay. They also studied the expression of apoptosis related genes such as Bcl-2, Bcl-XL, Bax and p53 in comparison to 18s housekeeping gene using reverse transcriptase-qPCR. The results from the qPCR confirmed the significant cytotoxicity and growth inhibitory activity of the methanolic extract of *F. szowitsiana*. This suggests its high potential for further clinical evaluations (Soltanzad *et al*., 2012).

Anti-inflammation property: Inflammation is a biological response initiated by innate immune response in an individual against harmful stimuli such as pathogen. It is also common condition present in many diseases such as cardiovascular diseases and diabetes mellitus (Mueller *et al*., 2010). It can be related to the excessive production of Nitric Oxide (NO) which initiates leucocytes recruitment (Laroux *et al*., 2001). Study by Kohno *et al*. (2011) proved that one of the terpenoid coumarins isolated from *F. szowitsiana*, methyl galbanate, demonstrated marked reduction of NO production in lipopolysaccharide (LPS)- or interferon-γ (IFN-γ)-stimulated RAW264.7 macrophage cells. From their findings, methyl galbanate treated RAW264.7 cells exhibited decreased level of LPS/IFN-γ-induced iNOS mRNA expression. Besides, methyl galbanate was capable of preventing NO-induced apoptosis in neuronally differentiated tsAM5NE cells (Kohno *et al*., 2011).

Antioxidant and anti-genotoxicity property: Reactive Oxygen Species (ROS) had been recognized to enhance the effects of inflammation via activation of inflammatory cascades (Conner and Grisham, 1996). Thus, discovery of the capability of *F. szowitsiana* in reducing ROS supports its anti-inflammation property as well. Soltani *et al*. (2010). demonstrated antioxidant capacity in auraptene isolated from *F. szowitsiana*. Auraptene was proved to decrease genotoxicity of H_2O_2 and its activity was higher than ascorbic acid. They suggest that auraptene suppress the generation of superoxide anion due to the presence of prenyl moiety (Soltani *et al*., 2010). The antioxidant property of *F. szowitsiana* was further supported by Gooshchi *et al*. (2012). In their study, antioxidant activity of the methanol extract of *F. szowitsiana* was proved by using DPPH (1,1-diphenyl-2-picryl-hydrazyl) assay where it demonstrated remarkable radical scavenging activity (8.85×10^{-2} mg mL^{-1}) comparable with rutin (5.12×10^{-2} mg mL^{-1}) (Gooshchi *et al*., 2012).

Anti-microbial property: Human leishmaniasis is a severe parasitic infection, caused by different species of *Leishmania*, a genus of trypanosomatid protozoa, with high mortality and morbidity rates in Asia, Africa and Latin. These intracellular pathogens can accumulate in dogs, rodents and other small mammals and are normally transmitted via mosquitoes from *Lutzomia* and *Phlebotomus* genera. Although leishmaniasis is difficult to treat due to the intramacrophagic location of the infectious form, many natural products have been reported to show anti-leishmanial activity. Due to the side effects of the alternative drugs used for leishmaniasis treatment, they have been replaced over the last few years, by plant extract and plant-derived compounds such as lignans, chalcones, naphthoquinones, alkaloids, triterpenoids and neolignans (Sauvain *et al*., 1996;

Balana-Fouce *et al*., 1998; Torres-Santos *et al*., 1999; Kayser *et al*., 2000; Barata *et al*., 2000; Camacho *et al*., 2000; Delorenzi *et al*., 2001; De Carvalho and Ferreira, 2001).

Iranshahi *et al*. (2008) isolated a number of compounds, as shown in Table 1 and evaluated the inhibitory activity of the acetone extract of *F. szowitsiana* roots, prenylated coumarins, szowitsiacoumarin A and szowitsia coumarin B, auraptene, umbelliprenin and galbanic acid against promastigotes of *L. major* compared with amphotericin B, as the positive control (Iranshahi *et al*., 2008). They employed stationary-phase promastigotes to evaluate the anti-leishmanial activity of the compounds via *in vitro* leishmanicidal assay (Jaafari *et al*., 2006). The acetone extract and all of the evaluated compounds indicated inhibitory activity against *L. major* promastigotes, especially umbelliprenin and auraptene which efficiently inhibited the parasite at IC_{50} values of 13.3 μM and 17.1 μM, respectively (Iranshahi *et al*., 2008). Coumarins and auraptene had been previously reported to show anti-leishmanial and growth inhibitory activities against the tropical parasite, *L. major* (Oketch-Rabah *et al*., 1997; Bravo *et al*., 1999; Napolitano *et al*., 2004) .

Modulation of antibiotic activity: Antibiotics include a substantial portion of medications, frequently used in modern medicine. The most significant problem associated with application of antibiotics is the ability of some important community and hospital-acquired pathogens, to acquire resistance to these therapeutic agents. The upward trend in the existence of resistant Gram-positive bacteria affirms the urgent need for development of new drugs and/or a combination of different therapies to control the resistant pathogens (Bazzazz *et al*., 2009). During the recent decades, many investigations on combinations of plant extracts and antibiotics have been conducted in order to find a solution for the problem of emerging resistance in clinical isolates.

Shahverdi *et al*. (2007) showed that the combination of cephalexin or penicillin G with galbanic acid isolated from from the acetone extract of *F. szwotsiana* roots demonstrated marked decrease in the MIC of the two antibiotics against *S. aureus* (Shahverdi *et al*., 2007). Later, Bazzazz *et al*. (2009), also demonstrated a reduction of MIC by antibiotics ciprofloxacin, methicillin and tetracycline against resistant isolates of *S. aureus* with galbanic acid from *F. szwotsiana*. Meanwhile, no inhibitory effect was observed on high concentration of galbanic acid. This suggests that the positive inhibitory effects demonstrated could be due to the combination of antibiotics and galbanic acid (Bazzazz *et al*., 2009).

CONCLUSION

Different medicinal potentials of *F. szwotsiana* in various diseases have been reported by many investigators. However, there is a definite requirement of more detailed mechanistic and clinical studies on the mechanisms of these properties. The current state of research on *F. szwotsiana* implicates great potential of the isolated bioactive compounds in treating diseases. With the advancement in medicinal chemistry and bioinformatics, the ethnomedicinal usage of *F. szwotsiana* can be scientifically explained and proved through *in vitro* or *in vivo* studies and may consequently be developed as potential plant-based drugs.

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