Cytotoxic activity of the genus *Ferula* (Apiaceae) and its bioactive constituents

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**Abstract**

**Objective:** The genus *Ferula* L. includes perennial flowering plants belonging to the Apiaceae family. This genus is a rich source of biologically active phytochemicals such as sulfur-containing derivatives, coumarins, sesquiterpenes, sesquiterpene lactones, sesquiterpene coumarins, glucuronic acid, galactose, arabinose, rhamnose, and daucane esters. Over the last decade, considerable attention has been paid to biological activities of these compounds; it is assumed that the most prominent biological features of the genus *Ferula* are their cytotoxic effects. This article discusses cytotoxic activity of the genus *Ferula* and their important compounds.

**Materials and Methods:** In this mini-review article, papers published from 1990 to April 2016 were included and the following information was discussed; cytotoxic activity of the genus *Ferula* and their important compounds, the type of cell line used *in vitro*, concentrations of the extracts/active compound that were used, and the underlying mechanisms of action through which *Ferula*-related chemicals induced cytotoxicity. In addition, we explained different mechanisms of action through which the active constituents isolated from *Ferula*, could decrease cellular growth.

**Conclusion:** It is highly recommended that potent and effective compounds that were isolated from *Ferula* plants and found to be appropriate as adjuvant therapy for certain diseases, should be identified. Also, the versatile biological activities of sesquiterpene coumarins suggest them as promising agents with a broad range of biological applications to be used in the future.

**Keywords:**
- Apiaceae;
- *Ferula*
- Biological activity
- Cytotoxicity
- Umbelliprenin
- Sesquiterpene coumarin
- Farnesiferol C.

Please cite this paper as:
Iranshahi M, Rezaee R, Najaf Najafi M, Haghbin A, Kasaian J. Cytotoxic activity of the genus *Ferula* (Apiaceae) and its bioactive constituents. Avicenna J Phytomed, 2018; 8 (4): 296-312.

**Introduction**

The genus *Ferula* includes perennial flowering plants belonging to the family Apiaceae (Umbelliferae). This genus consists of about 170 species which are distributed worldwide. Out of 30 species of *Ferula* that could be found in Iran, 16 plants are endemic. Different species of the genus *Ferula* are broadly distributed in arid areas from the eastern Mediterranean regions to central Asia (Gholami and
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Shamsara, 2016; Karimi et al., 2010; Nazari and Iranshahi, 2011; however, some Ferula species are found in arid regions of temperate Eurasia, in the Canary Islands and in North Africa (e.g. Tunisia) (Znati et al., 2014). Different species of the genus Ferula are regarded as rich sources of biologically active phytochemicals such as sulfur-containing derivatives, coumarins, coumarin esters, sesquiterpenes, sesquiterpene lactones, sesquiterpene coumarins, glucuronic acid, galactose, arabinose, rhamnose, and daucane esters (Figure 1) (Asghari et al., 2016; Maggi et al., 2016; Nazari and Iranshahi, 2011; Razavi et al., 2016).

Some species of the genus Ferula have therapeutic properties such as contraceptive, antipyretic, smooth-muscles relaxant and aphrodisiac activities (Nazari and Iranshahi, 2011; Yaqoob et al., 2016). Also, several Ferula species are well-known because of their applications in the treatment of various diseases. For example, F. persica root extract possesses antispasmodic, carminative, laxative and expectorant properties and has been used for the treatment of diabetes and high blood pressure (Razavi and Janani, 2015). F. assa-foetida exhibits anti-carcinogenic properties and has protective activities against free radical-mediated diseases (Gamal-Eldeen and Hegazy, 2010). Iranshahi et al. reported that F. assa-foetida has anti-leishmanial activity against promastigotes (Iranshahi et al., 2007). Moreover, Ferula species have been used in traditional medicine for the treatment of skin infections, hysteria and stomach disorders. Also, a number of Ferula species has been utilized as febrifuge and carminative agents and for relaxation of tracheal smooth muscles (Gamal-Eldeen and Hegazy, 2010). F. assa-foetida and F. gummosa are two famous species of Ferula in Iranian folk medicine. Additionally, some Ferula species are well-known as important sources of aromatic resins and are employed in cosmetic industries (Kanani et al., 2011).

Phytochemicals obtained from the species of Ferula are used in traditional medicine for the treatment of various diseases such as digestive disorders, rheumatism, headache, neurological disorders, arthritis, dizziness and dysentery. Galbanum, the aromatic gum resin obtained from F. gummosa, has been traditionally used as a tonic, anticonvulsant, and emmenagogue agent (Iranshahi et al., 2010). Moreover, asafoetida as the dried latex (gum oleoresin) exudates from the rhizome or tap root of F. assa-foetida, has been traditionally used for the treatment of various diseases including asthma and gastrointestinal disorders as well as removal of intestinal parasites. Asafoetida has also been known to possess antifungal, anti-diabetic, anti-inflammatory, anti-mutagenic and antiviral activities (Iranshahy and Iranshahi, 2011; Mahendra and Bisht, 2012).

A number of sesquiterpenes obtained from the species of Ferula roots, revealed antibacterial, antifungal, cytotoxic, antioxidant, and hormonal activities as well as P-glycoprotein inhibitory and immunomodulatory effects (Miski, 2013). Sanandajin and ethyl galbanate, the two sesquiterpene coumarins isolated from F. pseudalliacea root extract have shown potent antibacterial activities and are being used in pharmaceutical and food industries (Dastan et al., 2016).

In this review, we focused on cytotoxic activity of Ferula plants reported from 1990 to April 2016.
Group A - Sulfur-containing compounds and foetitiophene derivatives

Group B - Sesquiterpene lactones
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**Group C - Sesquiterpene coumarins**
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Figure 1. Chemical structure of some constituents of Ferula categorized in groups A-E.

**Cytotoxicity**

Ferulenol, a prenylated 4-hydroxycoumarin isolated from *F. communis*, exerted dose-dependent cytotoxicity against various human tumor cell lines. It stimulated tubulin polymerization *in vitro*, inhibited the binding of radio-labeled colchicine to tubulin, re-arranged cellular microtubule network into short fibres and altered nuclear morphology (Bocca et al., 2002). In another study, the cytotoxicity of ferulenol on human breast cancer (MCF-7), colon cancer (Caco-2), ovarian cancer (SKOV-3) and leukemic (HL-60) cells was evaluated; based on the results, ferulenol showed significant cytotoxic effects at concentrations of 10 nM, 100 nM and 1µM, against these cancer cell lines (Nazari and Iranshahi, 2011). Conferone is another sesquiterpene coumarin isolated from *Ferula* root extract. Barthomeuf et al. (2006) showed that 10μM of conferone enhances the cytotoxicity of vinblastine in MDR1-transfected Madin-Darby canine kidney (MDCK-MDR1) cells (Barthomeuf et al., 2006). Additionally, conferone enhanced the cytotoxicity of cisplatin and vincristine in 5637 cells (Neshati et al., 2012; Neshati et al., 2009). In another study, conferone
exhibited moderate cytotoxicity against CH1 (human ovarian carcinoma) and A549 (human nonsmall cell lung cancer) cells (Valiahdi et al., 2013). Also, umbelliprenin, a prenylated coumarin synthesized by various Ferula species, showed cytotoxic activity by inhibition of the growth of human M4Beu metastatic pigmented malignant melanoma cells through induction of cell cycle arrest in G1 and caspase-dependent apoptosis (Lourenco et al., 2012). Khaghanzadeh et al. (2012) studied umbelliprenin cytotoxicity in two different types of lung cancer cell lines (i.e. QU-DB and A549). Their results revealed that IC\textsubscript{50} values for QU-DB and A549 were 47±5.3 and 52±1.97 μM, respectively (Khaghanzadeh et al., 2012). Also, an investigation on umbelliprenin nanoliposomes revealed that liposomal umbelliprenin possesses time and concentration-dependent cytotoxicity on melanoma cell line (Ramezani et al., 2014). Additionally, umbelliprenin showed antigenotoxic properties in human peripheral lymphocytes, probably due to its prenyl moiety (Soltani et al., 2009). In another investigation, aurapten, a prenylated coumarin isolated from Ferula, exerted cytotoxic effects against MCF-7 cell line (IC\textsubscript{50}=59.7 μM) (Mousavi et al., 2015). Furthermore, stylosin and tschimgine (monoterpenes isolated from Ferula ovina) showed cytotoxic activities against human melanoma cell line SK-MEL-28 (Valiahdi et al., 2013). Also, Rassouli et al. (2011) reported the cytotoxic and apoptosis-inducing effects of stylosin (Rassouli et al., 2011).

Feselol and mogoltacin are two biologically active sesquiterpene coumarins isolated from root extracts of Ferula species that showed cytotoxic properties. For example, a combination of 40 mg/mL vincristine and 16 mg/mL mogoltacin increased the cytotoxicity of vincristine by 32.8%, in human transitional cell carcinoma (TCC) cells (BehnamRassouli et al., 2009). Similar results were found for feselol, a sesquiterpene coumarin isolated from the fruits of F. badrakema (Mollazadeh et al., 2010). Also, a combination of feselol and mogoltacin enhanced the cytotoxicity of cisplatin in 5637 cells (human bladder carcinoma cell line) (Mollazadeh et al., 2011; Rassouli et al., 2011). Hanafi-Bojd et al. (2011) showed that farnesiferol A and galbanic acid, two sesquiterpene coumarins isolated from Ferula species, increased verapamil cytotoxicity (Hanafi-Bojd et al., 2011). In another study, sanandajin, farnesiferol B, and kamolonol acetate displayed cytotoxic activities against HeLa cells with IC\textsubscript{50} values of 2.2, 6.7, and 4.9 μM, respectively (Dastan et al., 2014). Kasaian et al. (2015) revealed that sesquiterpene coumarins isolated from Ferula species exert different cytotoxic activities. Also, they reported that farnesiferol B, farnesiferol C and lehmferin reverse doxorubicin-resistance properties of MCF-7/Adr cells (Kasaian et al., 2015).

Methyl caffeate, a compound isolated from F. lutea showed cytotoxic effects, with IC\textsubscript{50} values of 22.5±2.4, 17.8±1.1 and 25±1.1 μmol/L against HCT-116 (human colon carcinoma cell line), IGROV-1 and OVCAR-3 (human ovarian cancer cell line), respectively (Znati et al., 2014). Also, kamolonol, 4′-hydroxy kamolonol acetate and farnesiferon B, the three sesquiterpene coumarins isolated from the roots of F. pseudalliacea, displayed cytotoxic activity against HeLa cells, with IC\textsubscript{50} values of 3.8, 4.5, and 7.7 μM, respectively (Dastan et al., 2014). However, Ghannadi et al. (2014) reported that kellerin, an active compound of F. assa-foetida, had no cytotoxic effect against Vero cells up to the concentration of 10 μg/mL (Ghannadi et al., 2014). Galbanic acid, the other sesquiterpene coumarin isolated from F. szowitsiana, inhibited A549 growth with an IC\textsubscript{50} value of 62 μM following 48hr treatment (Eskandani et al., 2015). Chitsazian-Yazdi et al. (2015) investigated 4 new foetithiophene compounds namely, foetithiophene C, foetithiophene D, foetithiophene E and foetithiophene F isolated from F. foetida.
They revealed that these compounds have no significant cytotoxic activities (IC\textsubscript{50} values>100 mM) against MCF-7 and K562 cancer cells (Chitsazian-Yazdi et al., 2015). Ferutinin is a natural product isolated from \textit{F. ovina} possesses apoptosis-inducing effects. Also, ferutinin analogues synthesized by esterification of jaeschkenadiol using different acids, have exhibited potent inhibitory activity against MCF-7 with an IC\textsubscript{50} value of 1 μM (Matin et al., 2014; Safi et al., 2015).

A number of sesquiterpene lactones isolated from \textit{F. oopoda} showed significant cytotoxicity. For example, dehydrooopodin revealed significant cytotoxicity with IC\textsubscript{50} values of 5 and 15 μM against K562 and MCF7 cancer cell lines, respectively (Kasaian et al., 2014).

Moreover, the cytotoxicity of dehydrooopodin and oopodin, two sesquiterpene lactones isolated from \textit{F. varia} were tested against KB (human epidermoid carcinoma of the nasopharynx), K562 (leukemia), MCF7, and COLO 205 (coloncarcinoma) cell lines, as well as the multidrug-resistant human cancer cell lines KB-C2 (colchicine-resistant KB) and K562/ADR (Adriamycin-resistant K562). These compounds showed moderate cytotoxicity with IC\textsubscript{50} values ranging from 24.7 to 56.9 μg/mL (Suzuki et al., 2007).

Cytotoxicity of some sesquiterpene coumarins isolated from \textit{F. sinkiangensis} was investigated by Li et al., 2015. They found that these sesquiterpene coumarins had selective cytotoxic activity against HeLa and AGS cancer cell lines, with IC\textsubscript{50} values of 12.7-226.6 μM (Li et al., 2015).

In 2006, it was reported that compounds isolated from \textit{F. assa-foetida} have potent and specific NF-κB-inhibiting properties, but their cytotoxicity were negligible (Appendino et al., 2006).

Chimgin and chimganin, two monoterpenoid compounds isolated from \textit{F. szowitsiana}, showed cytotoxic activities. Chimgin showed IC\textsubscript{50} values of 45.2, 67.1 and 69.7 μM and chimganin showed IC\textsubscript{50} values of 28, 74 and 30.9 μM for MCF-7, HepG2 and MDBK cancer cell lines, respectively. These values were just slightly lower than those of tamoxifen which was used as positive control (Sahranavard et al., 2009).

In a number of investigations, \textit{Ferula} root extracts and fractions have been studied. Eslami et al. (2015) showed that \textit{F. gummosa} extract has specific cytotoxic effects mainly against MCF7 and oral cancer cell lines (Eslami et al., 2013; Gudarzi et al., 2015). Elouzi et al. (2008) proved that petroleum extract of \textit{F. hermonisat} the concentration of 0.125 mg/ml, causes 50% cell death (Elouzi et al., 2008).

The extract of \textit{F. szowitsiana} root was shown to be active against three cancerous (MCF7, HepG2 and WEHI164) and one normal (MDBK) cell lines. In another study, the cytotoxicity of some of the Iranian medicinal \textit{Ferula} species was examined and all the extracts and oleo-gum resins of \textit{F. assa-foetida} showed dose-dependent cytotoxicity (Bagheri et al., 2010).

Hajimehdipoor et al. (2012) investigated the cytotoxic effects of \textit{F. persica} and \textit{F. hezarlalezarica}, two endemic \textit{Ferula} species of Iran, against MCF7, HepG2, HT29 and A549 (adenocarcinomic human alveolar basal epithelial cells), cancer cell lines. They revealed that hexane and chloroform fractions of these plants have cytotoxic effects at concentration up to 100 μg/ml. They also reported that the cytotoxicity of \textit{F. persica} extracts was higher than that of \textit{F. hezarlalezarica} extracts (IC\textsubscript{50}: 22.3-71.8 μg/ml for \textit{F. persica} and 76.7-105.3 μg/ml for \textit{F. hezarlalezarica}) (Hajimehdipoor et al., 2012).

In an investigation, \textit{F. assa-foetida} extract displayed neuroprotective effects in a glutamate-induced neurotoxicity model (Tayeboon et al. 2013). In another study, researchers reported the cytotoxic activities of the extracts and fractions of \textit{F. szowitsiana}, \textit{F. hirtella} and \textit{F. oopoda} against MCF-7, HT-29, A549 and HepG2.
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cancer cell lines. Based on their data, n-hexane and chloroform fractions of F. szowitsiana and F. hirtella were cytotoxic, probably due to the presence of non-polar/semi-polar constituents (Hamzeloomoghdam et al. 2013). Furthermore, the cytotoxic properties of the n-butanol extract of F. lutea with an IC$_{50}$=40 µg/ml against K562 (leukemia cell line) was reported (Znati et al., 2014).

The cytotoxicity of F. assa-foetida extract on HOS CRL, an osteosarcoma cell line was also investigated. The results of this investigation showed that the cytotoxic activity of F. assa-foetida extract is dependent on the type and concentration of the solvent. Moreover, the methanol extract possessed more marked cytotoxic effects than the ethanol extract (Shafri et al., 2015). In another study, results of MTT assay of F. assa-foetida extract against an osteosarcoma cell line (HOS CRL-1543) showed that this activity is dependent on the type of solvent (methanolic>ethanolic) and its concentration (higher methanolic content>lower methanolic content) (MohdShafri et al., 2015).

Gudarzi et al. (2015) showed anti-proliferative activity of ethanolic extract of F. gummosa seed, which was probably related to the presence of bioactive compounds like coumarins and terpenoids (Gudarzi et al., 2015). Additionally, cytotoxicity of hydroalcoholic extract of F. gummosa root was investigated on GP-293 cell line and primary cultured human stromal-vascular cells. The viability of human stromal-vascular cells following treatment with F. gummosa extract 400 mg/mL (60±6.5% of the control, p<0.01) and 800 mg/mL (14±1% of control, p<0.001) were significantly decreased. Also, the F. gummosa root extract reduced the viability of GP-293 cells at concentration of 750 mg/mL (8.8±0.35%, p<0.001) (Ghorbani et al., 2016).

Some other cell-based assays

Umbelliprenin and auraptene, two prenylated coumarins isolated from F. szowitsiana revealed cytotoxic properties. Umbelliprenin showed the highest inhibitory activity against M4Beu melanoma cell line (IC$_{50}$=12.4±0.5 µM) compared to cisplatin (23.1±0.8 µM) (Paydar et al., 2013; Shakeri et al., 2014). Ziai et al. (2012) studied apoptosis-inducing activities of umbelliprenin in Jurkat T-CLL and Raji B-CLL cell lines. Their results showed that umbelliprenin induced apoptosis in leukemic cells in a dose- and time-dependent manner; also, CLL (Chronic lymphocytic leukemia) cells were more susceptible to umbelliprenin-induced cell death as compared to normal peripheral blood mononuclear cells (PBMCs) (Ziai et al., 2012). In another study, Barthomeuf et al. (2008) showed that umbelliprenin induces caspase-dependent apoptosis (IC$_{50}$=12.3 µM) (Barthomeuf et al., 2008). Gholami et al. (2013) investigated the effect of umbelliprenin on pro-apoptotic caspases (caspase-8 and -9) and anti-apoptotic Bcl-2 family protein in Jurkat cell line. They revealed that umbelliprenin activates intrinsic and extrinsic pathways of apoptosis by activation of caspase-8 and caspase-9, respectively. They also found that umbelliprenin inhibits Bcl-2 protein. Furthermore, umbelliprenin induced apoptosis in Jurkat cells through a caspase-dependent pathway (Gholami et al., 2013).

Ferulenol, a prenylated coumarin from F. communis (Umbelliferae) exhibited tubulin-polymerizing activity. Under Ca$^{2+}$-free conditions, ferulenol appeared to be equipotent as Taxol in promoting tubulin assembly (Altmann and Gertsch, 2007). Recently, it was shown that conferone 20 µM induces cell arrest and cell death through both apoptosis and necrosis in HT-29 cells (Cheraghi et al., 2016).

Galbanic acid, a sesquiterpene coumarin isolated from Ferula species showed cytotoxic activities. Galbanic acid inhibited the growth of prostate cancer cells via decreasing androgen receptor abundance (Kasaian et al., 2014). Also, galbanic acid induced apoptosis in H460 cells via caspase
activation and Mcl-1 inhibition in H460 cells; therefore, it could be considered a potent cytotoxic agent against non-small cell lung carcinoma (Oh et al., 2015). Researchers also revealed that galbanic acid has anti-angiogenesis effects (Kim et al., 2011).

Diversin, a natural prenylated coumarin isolated from Ferula roots, revealed cytotoxic activity as well as cell-cycle-inhibitory and apoptosis-inducing effects on bladder carcinoma cells (Haghighitalab et al., 2014).

Umbelliferone, a naturally occurring coumarin derivative isolated from F. communis, has been suggested as an effective cytotoxic compound against HepG2 cell line. Furthermore, umbelliferone exhibited apoptosis-inducing activity in HepG2 cells in a concentration-dependent manner (0-50 μM) (Yu et al., 2015).

Huang et al. (2013) investigated two new terpenoid benzoates namely, syreiteate A and syreiteate B, isolated from the roots of F. dissecta. Their results proved that syreiteate A and syreiteate B have potent growth inhibitory activity against cervical cancer HeLa cell line with IC₅₀ values of 13.2 and 19.3 μM, respectively (Huang et al., 2013).

Ferutinin, a natural sesquiterpene of Ferula, showed apoptosis-inducing activities in cancerous cells by induction of sub-G1 peak as revealed by PI staining (Arghiani et al., 2014). Researchers also showed that ferutinin has apoptotic effects in human Jurkat T-cell line (Macho et al., 2004).

Nano-based formulation of farnesiferolC isolated from the resin of F. assa-foetida L. exerted anti-angiogenic activity (Lee et al., 2010).

Mousavi et al. (2015) reported aurapteine apoptotic effects in MCF-7 cell line (IC₅₀ = 59.7 μM). They revealed that aurapteine induced a sub-G1 peak in the flow cytometry histogram of treated cells compared to control cells. In this study, DNA fragmentation was suggested as one of the underlying mechanisms of aurapteine-induced apoptosis. Also, western blot analysis showed that aurapteine significantly up-regulated Bax expression in MCF-7 cells compared to untreated controls (Mousavi et al., 2015).

DAW22, a natural sesquiterpene coumarin isolated from F. ferulaeoides (Steud.) Korov. Induced C6 glioma cell apoptosis and endoplasmic reticulum (ER) stress, via mitochondrial and death-receptor-mediated pathways (Zhang et al., 2015).

Dietary phytochemicals present in F. assa-foetida, like luteoline, ferutinin and ferutidine, induced apoptosis and inhibited cell proliferation at the level of DNA synthesis (in S-phase) (Bansal et al., 2012; Matin et al., 2014). F. assa-foetida extract exerted anti-apoptotic activity in cerebellar granule neurons by induction of cell cycle arrest in G0/G1 phase; therefore, F. assa-foetida extract was suggested to be used against neurologic disorders (Tayeboon et al., 2013).

Gharaei et al. (2013) revealed that F. gummosa Boiss. extracts exerted anti-proliferative as well as apoptosis-inducing effects in a human gastric adenocarcinoma cell line (AGS). They also reported that F. gummosa extracts inhibited AGS cell line proliferation in a dose-dependent manner with IC₅₀ values of 37.47 μg/mL for flower and 32.99 μg/mL for leaf extracts. F. gummosa extracts also induced apoptosis, as reflected by DNA fragmentation and plasma membrane translocation of phosphatidyl serine (Gharaei et al., 2013). F. gummosa flower and leaf extracts inhibited angiogenesis in a concentration-
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dependent manner (10-30 µg/ml), reflecting the possible presence of anti-angiogenic compounds (Mirzaaghaei et al., 2014).

In another study, it was reported that *F. assa-foetida* and *F. gummosa* exert cytotoxic effects. The cytotoxic effects of *F. assa-foetida* were mediated through three mechanisms including inhibition of mutagenesis, DNA destruction and cancer cell proliferation, while *F. gummosa* exerted its effects via cell cycle arrest and induction of apoptosis (Asadi-Samani et al., 2015).

Cytotoxic activity of sesquiterpene coumarins isolated from *F. nartex* was examined by Alam et al. (2016). These researchers reported that n-hexane fraction of *F. nartex* extract shows significant cytotoxic activity against PC3 cancer cells with an IC$_{50}$ value of 5.43 ± 0.24 µg/ml (Alam et al., 2016). *F. vesceritensis* extract, as a new natural source of lapiferin, showed promising specific cytotoxic activity against human breast cancer cells. The cytotoxic activity was shown to be mediated through induction of apoptosis. Lapiferin evoked multiple pathways involving enhancement of DNA fragmentation, activation of caspases and induction of histone acetylation, all triggering apoptosis (Gamal-Eldeen and Hegazy, 2010).

The ethyl acetate fraction of *F. sinkiangensis* extract revealed efficient inhibiting effects on tumor cells proliferation and enhanced the apoptosis rate in tumor cells (Zhang et al., 2015).

**Mechanisms of action**

It has been found that natural agents with cell-based properties can be divided into two categories of cytotoxic and/or anti-proliferative compounds (Keskin et al., 2000). For example, sesquiterpene coumarins isolated from the *Ferula* genus, showed both growth inhibitory and cytotoxic activities in different cancerous cell lines (Ryuet al., 2001).

Umelliprenin has exerted anti-proliferative effects on M4Beu cells (human metastatic pigmented malignant melanoma cell line) through cell cycle arrest in G1 phase (Barthomeuf et al., 2008) and cytotoxic effects on A549 (human lung cancer cell line) via mitochondrial-dependent mechanisms (Barthomeuf et al., 2008; Khaghanzadeh et al., 2012).

It seems that two different mechanisms of cellular growth inhibition consist of lowering proliferation rate and induction of cellular death through apoptosis or necrosis.

Generally, Bcl-2 family proteins such as Bcl-2 protein and Bax protein, have important regulatory roles in apoptosis. Aldaghi et al. indicated that farnesiferol C and microlobin, two sesquiterpene coumarins isolated from *F. szowitsiana*, have greater binding affinity to Bax protein in comparison to Bcl-2 protein. These researchers assumed that the interaction between drugs and hydrophobic groove of Bax protein might result in conformational changes and insertion of Bax protein into mitochondrial membrane, consequently inducing Bax-dependent apoptosis (Aldaghi et al., 2016). In another study, RT-PCR analysis of Bax and Bcl-2 genes showed that dendrosomal form of farnesiferol C could suppress AGS cell proliferation, at least in part, via inducing apoptosis. Moreover, some recent research revealed that coumarin compounds could induce apoptosis by modulating Bax/Bcl-2 and caspase pathways (Gholami et al., 2013; Sadeghizadeh et al., 2008).

Cytotoxic activity of galbanic acid was mediated through inhibiting angiogenesis, the essential process required for tumor growth and metastasis. Galbanic acid significantly decreased vascular endothelial growth factor (VEGF)-induced proliferation and inhibited VEGF-induced migration and tube formation in human umbilical vein endothelial cells (HUVECs). These effects were accompanied by decreased phosphorylation of p38-mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK), and AKT, and
decreased expression of VEGFR targets endothelial nitric oxide synthase (eNOS) and cyclin D1 in VEGF-treated HUVECs (Kim et al., 2011). In another study, galbanic acid showed a promising inhibitory activity against farnesyltransferase (FTase), an essential enzyme needed for tumor growth in pancreas and colon cancers (Figure 2) (Cha et al., 2011).

**Table 1. Overview of the cytotoxic activities of Ferula species.**

| Plant Name | Important Compound | Biological activity | cell line | Tested concentrations (IC<sub>50</sub>) µg/mL | Mechanism of action | Reference |
|------------|--------------------|---------------------|-----------|---------------------------------|---------------------|-----------|
| *F. vescentensis* | Lapiferin | Cytotoxic Apoptotic | MCF7 | 1.285 | Anticancer activity Induction of apoptotic cell death through enhancement of DNA fragmentation, activation of caspases and induction of histone acetylation | Gamal-Eldeen and Hegazy, 2010 |
| *F. assa-foetida* | 8-acetoxy-5-hydroxy Umbelliprenin | Cytotoxic | A549 | 15.09 | Potent and specific inhibition of NF-κB | Appendino et al., 2006 |
| *F. assa-foetida* | Coumarin compounds | Cytotoxic | HepG2 | | Inhibition of mutagenesis, DNA destruction and cancer cells proliferation while increasing proteolytic enzymes activity | Asadisamani et al., 2015 |
| *F. gummosa* | Sesquiterpenes, coumarins | Cytotoxic | HepG2 | | Induction of cell cycle arrest and apoptosis | Asadisamani et al., 2015 |
| *F. assa-foetida* | Ferutinin | Cytotoxic | CT26 HT29 | 26 29 | Induction of apoptosis | Arghiani et al., 2014 |
| *F. communis* | Ferulenol | Cytotoxic | MCF-7 | 1 | Reorganization of the microtubule network in MCF-7 cells and alteration of nuclear morphology | Altmann and Gertsch, 2006 |
| *F. sinkiangensis* | Ethyl acetate Fraction Methyl caffeate | Cytotoxic | MCF7 | 9.0 mg/L | Inhibition of tumor cell proliferation | Zhang et al., 2015a |
| *F. lutea* | Dendrosomal farnesiferol C | Antiproliferative and Apoptotic | AGS (gastric cancer) | | Significant time- and dose-dependent suppression of AGS cells proliferation | Aas et al., 2015 |
| *F. szowitziana* | Kellerin | Antiviral | HSV-1 | | Reduction of viral titre of the HSV-1 DNA viral strains KOS | Ghannadi et al., 2014 |
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| Species       | Compound                                    | Cells/Cell Line       | IC50 IC50 IC50 | Effect                                                                 |
|---------------|---------------------------------------------|-----------------------|----------------|------------------------------------------------------------------------|
| F. pseudalliacea | Kamolonol, 4’-hydroxy kamolonol acetate and farnesiferon B | HeLa-60 | 3.8, 4.5, and 7.7 μM, respectively | Seemingly, these compounds interfere with fundamental processes of growth and metabolism of the cells. |
| F. lutea      | n-butan extract                            | K562                  | 40 μg/mL       | Low cytotoxicity compared to doxorubicin. Induction of a sub-G1 peak in the flow cytometry histogram, DNA fragmentation and apoptosis as well as up-regulation of Bax expression. |
| F. szowitsiana | Auraptenone                                 | MCF7                  | 59.7 μM        | Not-mentioned.                                                         |
| F. ovina      |                                            | MCF-7                 | 45.2 for Chimgin and 28 for Chimgain | Induction of apoptosis through ER stress and mitochondrial death-receptor mediated pathways. |
| F. sinkiangensis | DAW22                                       | C6 glioma cell         | 18.92 μM in 24h | Induction of apoptosis and cell-cycle arrestin G1/S phase.             |
| F. gummosa    | Ethanol extract                             | BHY (human oral squamous human lymphocytes) | 0.001±0.12 mg/mL in 72h | Induction of apoptosis and cell-cycle arrestin G1/S phase.             |
| F. szowitsiana | Umbelliprenin                               | MCF7, TCC and HFF-3   | 25 to 400 μM   | Inhibition of H2O2-induced DNA damage.                                 |
| F. ovina      | Ferutinin                                   | Human umbilical vein endothelial cells (HUVEC) | 1.1 ml/g/kg body weight | Inhibition of VEGFR1.                                                  |
| F. Narthex    | Sesquiterpenes coumarins                    | PC3 cells              | 14.07±4.014 μg/mL | Not mentioned.                                                         |
| F. badakema   | Mogoltacin                                  | HeLa cells             | 2.2 μM         | Not mentioned.                                                         |
| F. pseudalliacea | Sanandajan                                | TCC                   | (inhibition 63.5%) | Anti-cholinesterase activity.                                          |
| F. ovina      | Tschimine                                  | Red blood cell (RBC)   | 29, 24 and 36 μg/ml, respectively | Inhibition of P-glycoprotein-mediated drug transport. |
| F. nathex     | Sesquiterpenes coumarins                    | PC3 cells              | 14.07±4.014 μg/mL | Not mentioned.                                                         |
| F. oopoda     | Dehydrooopodin                             | MCF7 and K562         | 15 and 5pM, respectively | Not mentioned.                                                         |
| F. assa-foetida | Methanolic extract                        | MDA-MB-231 Cell Line  | 650 μg/mL in 72h | Not mentioned.                                                         |
| F. gummsa     | Ethanolic extract                          | Gastric, AGS           | 37.47 μg/mL    | Induction of apoptosis via induction of DNA fragmentation and plasma membrane translocation of phosphatidyl serine. |
| F. szowitsiana | Umbelliprenin                              | Jurkat T-CLL          |                | Induction of caspase-mediated apoptosis. Activation of intrinsic and extrinsic pathways of apoptosis by activation of caspase-9 and caspase-8. |
| F. szowitsiana | Umbelliprenin                              | QUDB and AS49         | 47±5.3 μM and 52±1.97 μM, respectively | Induction of apoptosis. |

**Conclusion**

Ferula plants are rich sources of phytochemicals such as sesquiterpene coumarins, sesquiterpene lactones and sulfur-containing compounds. Over the last decade, considerable attention has been paid to investigate the potential cytotoxic activities of Ferula (Apiaceae) plants and their main constituents. This review aimed to highlight cytotoxic activities of Ferula species and their phytochemicals (Table 1). We also discussed different mechanisms through which active compounds isolated from Ferula species decrease cellular growth or induce cell death.

It is assumed that the most prominent biological features of the genus Ferula are their cytotoxic effects. Previous reports proposed that Ferula phytochemicals have different activities. This probably suggests...
that much effort still remains to be made to identify potent and effective Ferula compounds that could be appropriate to be used as adjuvant therapy along with the conventional antibiotics. It is ultimately suggested that considering the versatile biological activities of sesquiterpene coumarins, these compounds may have an even broader range of biological applications in the future.

Acknowledgment
The authors are thankful to the Research Council of North Khorasan University of Medical Sciences, Bojnurd, Iran, for their support.

Conflict of Interest
The authors declare no conflict of interest.

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