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Botany, secondary metabolites, therapeutic effects and toxicity of *Ferula persica*: A review

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ABSTRACT

Background & Aim: *Ferula persica* is a medicinal plant belonging to the Apiaceae family and grows in some provinces of Iran, including Mazandaran, Tehran, Semnan, Alborz, and Qazvin. The plant is traditionally used as an expectorant, antispasmodic, anti-bloating and laxative, also it is used to treat indigestion with bloating and constipation, neurologic diseases, epilepsy, and various pain, especially joint pain. Due to the value and importance of *F. persica* in traditional medicine and its beneficial pharmacological effects, this review aimed to investigate the findings on the ethnobotany, phytochemistry, traditional uses, and pharmacological effects of this medicinal plant published up to 2022.

Experimental: The information and findings in this review were obtained via electronic search using Google Scholar, Pubmed, Science Direct, Wiley Online, and Taylor & Francis, as well as relevant books.

Results: Various studies have shown that *F. persica* contains secondary metabolites such as coumarin, sulfur-containing compounds, steroids such as stigma-esterol, sitosterol, monoterpene and sesquiterpene, also numerous pharmacological activities including antitumor, anti-Alzheimer, antiepileptic, analgesic, anti-inflammatory, antibacterial, and antigenotoxic, about the plant have been reported.

Recommended applications/industries: Due to high-value components, wide application in traditional medicine, and various pharmacological effects, *F. persica* may be addressed as a source of multiple herbal medicinal compounds.

1. Introduction

Medicinal herbs play an important role in traditional and modern medicine and have been used in order to human health care since ancient years (Fasihzadeh *et al.*, 2016; Ghasemi and Lorigooini, 2016; Rabiei *et al.*, 2015; Hoseinpour *et al.*, 2021). Various studies have shown the beneficial effects of these plants in many diseases including Alzheimer's (Rabiei *et al.*, 2014), atherosclerosis (Nasri *et al.*, 2013; Lorigooini *et al.*, 2014; Lorigooini *et al.*, 2015; Hosseinpour *et al.*, 2017), diabetes (Mirhoseini *et al.*, 2013; Baradaran *et al.*, 2013) and cancer (Shirzad *et al.*, 2013; Shirzad *et al.*, 2011). The results of these studies regarding the production of alternative drugs to replace synthetic drugs for these diseases have been promising. Iran also has a long history of using herbal remedies in traditional medicine. It is said that 7500 species of medicinal plants have been found in Iran (Rezazadeh *et al.*, 2003).

Ferula persica has been used in traditional medicine as an antispasmodic, anti-bloating, and laxative agent to treat indigestion with bloating and constipation and has also been used in the treatment of neurologic

diseases, epilepsy, and various pains, especially joint pain (Samsam shariat, 2007; Zargari, 1988). Recent studies have led to the discovery of some biological activities of *F. persica*, including antimicrobial, antitumor, anti-inflammatory, and morphine-related side effects reducing. In January 2017, a review article on evidence regarding the phytochemicals and pharmacological impact of *F. persica* reported in 2016 was published (Sattar and Iranshahi, 2017).

The present study examined the pharmacological effects of *F. persica* more extensively by 2022, fully explaining its use in traditional medicine, describing the secondary metabolites in its essential oil and extract separately, as well as its toxicity that has recently been evaluated. This review aims to address the findings on the botany, secondary metabolites, applications in traditional medicine, pharmacological effects, and toxicity of *Ferula persica* from 2000 to 2022.

2. Materials and Methods

To conduct this review, firstly, botany & traditional medicine applications of *F. persica* are addressed. Subsequently, the pharmacological effects of this medicinal plant in various studies reviewed. For this purpose, the articles indexed in PubMed, Google Scholar, Science Direct, Wiley Online, and Taylor & Francis and published before 2023 were retrieved. Articles in which the secondary metabolites, biological activities and toxicity of *F. persica* had been depicted, were selected.

3. Botany

The genus *Ferula* belongs to the Apiaceae family, consisting of 260 species extending from Central Asia to the west across the Mediterranean region to Northern Africa (Mozaffarian, 1983; Evans, 1989; Mozaffarian, 1998). The genus *Ferula* in Iran includes 30 species, half of which are native to Iran (Mozaffarian, 1983; Mozaffarian, 1998), and half of these species are distributed in Anatolia, Central Asia, Afghanistan, Turkey, China, and the former Soviet Union, as well (Mozaffarian, 1998).

These species include perennial plants frequently found in mountainous areas and occasionally occurring in deserts. The endemic species of the genus in Iran, include *Ferula asafetida*, *Ferula gummosa* Boiss, and *Ferula persica* willd. *F. asafetida* and *F. gummosa* often occur in the highlands of the Iranian mountains, especially in the northern highlands and the surrounding areas of Damavand (Zargari, 1988; Akhondzadeh, 2000).

F. persica has two varieties, i.e., *F. persica* var. *latisecta* and *F. persica* var. *persica*. The two varieties differ in the leaf size such that *F. persica* var. *latisecta* has broad leaves, and its lip (end fragments) is about 6-10 mm, while it is about 3 mm in *F. persica* var. *persica*. The stem height of this species is about 100-150 cm, and its petals are yellow, green-white, and long yellow or oval with a fully curved apex (Mozaffarian, 2004).

This plant is monocarpic, i.e., disappears after flowering and fruiting (Mozaffarian, 1998). Areas of distribution of *F. persica* include Mazandaran, Tehran, Semnan (Damghan), Alborz, and Qazvin provinces (Jalili and Jamzad, 1999).

4. Traditional medicine uses

Traditional medicine uses *F. persica* gum and resin as an antispasmodic, anti-bloating, laxative, expectorant, to treat indigestion with bloating and constipation, neurologic disorders, epilepsy, and various pains, especially joint pain (Zargari, 1988; Samsam shariat, 2007). Other reports suggest that *F. persica* is used as an anti-hysteria for treating rheumatism and low back pain (Zargari, 1988; Eigner and Scholz, 1990; Afifi and Abu-Irmaileh, 2000). *F. persica* is also known to treat muscle spasms and ileum contraction (Mandegary *et al.*, 2004). This medicinal plant has also been reported as a hypotensive agent (Samsam shariat, 2007), and its root has been used to treat diabetes in traditional medicine (Afifi and Abu-Irmaileh, 2000).

F. persica has also been said to be a diuretic, alexipharmic, and emmenagogue (Musto, 2009), and is used to treat kidney stones, gout, and stomach worms (Mirheidar, 2003). One study reported that the edible form of *F. persica* that cooked with steam, is used as a spice for treating sinusitis, low back pain, pododynia, and heart oxygenating (Ahvazi *et al.*, 2012).

5. Secondary metabolites

Ferula species are rich in secondary metabolites classified into two parts: extract-derived and essential oil-derived.

5.1. Extract-derived secondary metabolites

The phytochemical investigations of extract of the seed, root, and aerial parts of different species of the genus *Ferula* have shown various compounds, including terpenes, glycosides of sesquiterpene coumarins, terpenoid compounds such as alpha-pinene and beta-pinene, alkaloids and cardenolides (Mandegary *et al.*, 2004; Iranshahi *et al.*, 2008a), the sulfur-containing compounds include asadisulphide and rutadisulfides (Iranshahi *et al.*, 2003), Umbelliprenin (Barthomeuf *et al.*, 2008) and phytosterols such as stigmasterol and sitosterol (Iranshahi *et al.*, 2008a). The names of isolated and identified compounds are listed in Table 1. The structural formula images of these compounds have already been given in Sattar and Iranshahi's review article (Sattar and Iranshahi, 2017).

5.2. Essential oil-derived secondary metabolites

In the aerial parts of *F. persica*, the relative frequency of monoterpene hydrocarbons is less than 10%, and that of oxygenated monoterpenes is around 15%, and in its root, about 25%. The frequency of sesquiterpene hydrocarbons in the aerial parts is less than 5%, and in the root, over 10%. The frequency of oxygenated sesquiterpenes in the aerial parts is negligible, at about 1% (Sahebkar and Iranshahi, 2010). In a study, the chemical composition of *F. persica* essential oil determined using Gas Chromatography. In this study, 61 compounds were identified, accounting for 93.7% of the total essential oil.

The main compounds of the essential oil obtained from the aerial parts of this plant include dill-apiol (57.3%), elemicin (5.6%), and limonene (4.4%) (Javidnia *et al.*, 2005). In another study, alpha-pinene (33.5%), camphene (11.7%), spathulenol (8.2%), and citronellyl acetate (5.3%) were identified in essential oil of aerial parts of the *F. persica* var. *persica*. In this study, the main compounds isolated from the essential oil of aerial parts of *F. persica* var. *Latisecta* were reported to be alpha-pinene (55%), camphene (20.5%), spathulenol (6%), and limonene (4.8%) (Kanani *et al.*, 2011).

Iranshahi *et al*. (2006) studied the essential oil of *F. persica* Wild var. *persica* root using GC and GC-MS and identified 39 compounds which represented 82% of the essential oil. Sulfur-containing compounds, including dimethyl trisulfide (18.2%), myristicin (8.9%), and dimethyl tetrasulfide (7.6%) were the main compounds (Iranshahi *et al.*, 2006).

In another study by Izadinia (2019), the phytochemistry of the essential oil of *F. persica* leaf and flower was evaluated using GC and GC-MS. Thirty one (94.4% of total essential oil) compounds were recognized in the essential oil of the leaf. α-pinene (19.7%), ß-pinene (8.3%), Menthol (8.3%), and Myrcene (6.8%) were the main components, and 12 compounds identified in the essential oil of flower (90.2% of total essential oil). α-pinene (22.6%), Bicyclogermacrene (17%), ß-phellandrene (16.8%), Spathulenol (8.4%), and Myrcene (7.5%) were the main component (Izadinia, 2019). No studies have yet been performed to isolate secondary metabolites from gum extracts or essential oils of this plant.

6. Pharmacological effects

Recent investigations have led to the discovery of certain new biological activities for the plants of the *Ferula* genus, including antimicrobial, antifungal, antiviral, anti-leishmaniasis, analgesic, anti-inflammatory, antiepileptic, antioxidant, antimycobacterial, inducing apoptosis in melanoma cancer cells, matrix metalloproteinase inhibitor, cancer preventing, microbial pigments formation inhibiting, antispasmodic and hypotensive (Sahebkar and Iranshahi, 2010), of which antimicrobial, antitumor, morphine-induced side effects lowering activities, etc. can be attributed to *F. persica*. The biological activities of the plants belonging to this genus are related at least partly to their essential oils (Sahebkar and Iranshahi, 2010).

Table 1. Secondary metabolites of different parts of *Ferula persica* extracts.

Secondary metabolite	Extraction solvent	Part of *F. persica*	References
Umbelliprenin	Chloroform	Root	Shahverdi *et al*. (2006); Iranshahi *et al*. (2004)
Badrakemone	Chloroform	Root and aerial parts	Shahverdi *et al*. (2006); Iranshahi *et al*. (2004)
Farnesiferol A	Chloroform	Root and aerial parts	Shahverdi *et al*. (2006); Aghbali *et al*. (2015); Iranshahi *et al*. (2004)
Farnesiferol B	Chloroform	Root	Iranshahi *et al*. (2004)
Gummosin	Chloroform	Root	Shahverdi *et al*. (2006); Iranshahi *et al*. (2004)
Persicasulphide A	Chloroform	Root	Shahverdi *et al*. (2006)
Persicasulphide B	Chloroform	Root	Shahverdi *et al*. (2006)
Farnesiferone A	Chloroform	Roots and aerial parts	Iranshahi *et al*. (2004)
Mogoltadone	Dichloromethane	Root	Valiahdi *et al*. (2013)
Persicaoside A	Chloroform and methanol	Root	Iranshahi *et al*. (2008a)
Persicaoside B	Chloroform and methanol	Root	Iranshahi *et al*. (2008a)
Persicaoside C	Chloroform and methanol	Root	Iranshahi *et al*. (2008a)
Persicaoside D	Chloroform and methanol	Root	Iranshahi *et al*. (2008a)
Sitosterol 3-O-b-glucoside	Chloroform and methanol	Root	Iranshahi *et al*. (2008a)
Stigmasterol 3-O-b-glucoside	Chloroform and methanol	Root	Iranshahi *et al*. (2008a)
t-butyl 3-[(1-methylpropyl)dithio]-2-propenyl malonate	Methanol	Root	Iranshahi *et al*. (2003)
t-butyl 3-[(1-methylthiopropyl) thio]-2-propenyl malonate	Methanol	Root	Iranshahi *et al*. (2003)
Ferulone C	n-hexane	Root	Razavi and Janani (2015)
Persicasulphide C	Chloroform	Root	Iranshahi *et al*. (2009a)

6.1. Cytotoxic and antitumor activity

Cancer is a set of disorders that cause high mortality in humans and has different types. Many studies have been done to introduce cheaper drugs with fewer side effects, especially with natural sources. Shahverdi *et al*. (2006) investigated the effect of persicasulphide B and umbelliprenin isolated from chloroform extract of *F. persica* var. *Persica* on producing matrix metalloproteinases by fibrosarcoma cell line using MTT. The results showed that these compounds had the highest inhibitory effect at a minimum toxic dose (10 µg/mL) (IC_{50}= 29.5 µg/mL). Matrix metalloproteinases are involved in physiological and pathological processes. There is some evidence that these enzymes are involved in tumor invasion (Shahverdi *et al.*, 2006).

Iranshahi *et al*. (2008) studied the effect of active ingredients (terpenoid coumarins) from different species of the *Ferula* genus on TPA-induced EBV EA activation. The results showed that Farnesiferol A with IC_{50}= 13.1 nM and badrakemone with IC_{50}= 13.3 nM were able to inhibit cell growth. Umbelliprenin and aurapten also significantly inhibited EBV-EA activity, indicating that they are valuable antitumor enhancers. The findings suggest that a prenyl component in terpenoid coumarins plays a vital role in antitumor action (Iranshahi *et al.*, 2008b).

In a study by Iranshahi *et al*. (2009), the prophylactic effect of umbelliprenin, a sesquiterpene coumarin, was evaluated on murine skin tumors *in vivo*. The results showed that umbelliprenin delayed the formation of papillomas by 9th week and reduced the number of tumors per mouse by 45%. In addition, the pattern of tumor progression was slower by treatment with umbelliprenin compared with curcumin as the reference drug. Therefore, umbelliprenin is a valuable cancer-preventing agent (Iranshahi *et al.*, 2009b). Khorramizadeh *et al*. (2010) studied the effect of umbelliprenin coated with Fe_3O_4 magnetic nanoparticles on the human fibrosarcoma cell line (HT-1080) *in vitro*. The results showed that the combination of umbelliprenin and Fe_3O_4 nanoparticles with IC_{50}=9 µg/mL, prevented cell proliferation (Khorramizadeh *et al.*, 2010).

Bagheri *et al*. (2010) evaluated the cytotoxicity of *Ferula* species on the brine shrimp (*Artemia salina*) as a model to assess overall cytotoxicity. The results indicated that the methanolic extracts of *F. diversivittata*, *F. persica*, *F. badrakema*, and *F. ovina* showed dose-dependent cytotoxicity with appropriate LC_{50} values in the range of 6 – 321 µg/mL. The highest cytotoxicity was reported for *F. badrakema* fruits and the lowest for *F. badrakema* roots (Bagheri *et al.*, 2010). P-glycoprotein is a member of the ATP-dependent membrane transport proteins that removes substrates from the cells through an ATP-dependent mechanism. Increased expression of P-glycoprotein in the tumor cells reduces intracellular drug concentration, reducing the cytotoxicity of a wide range of

chemotherapeutic agents. Accordingly, P-glycoprotein inhibitors are potential enhancers for the bioavailability of critical chemotherapeutics e.g., anthracyclines, taxanes, etc. (Krishna and Mayer, 2000). Different herbal secondary metabolites such as flavonoids, coumarins, terpenoids, alkaloids, and saponins can inhibit P-glycoprotein (Abdallah *et al.*, 2015). In this regard, the study of Hanafi-Bojd *et al.* (2011) showed that farnesiferol A (0.5 µg/mL) from *F. persica* and galbanic acid (5, 10 and 25 µg/mL) from *F. szowitsiana* with sesquiterpene coumarin structure, both of which were isolated from the root of the plant, could inhibit P-glycoprotein-dependent rhodamine 123 efflux in a doxorubicin-resistant (MCF_7/Adr) breast cancer cell line (Hanafi-Bojd *et al.*, 2011).

In a study by Kasaian *et al*. (2015), 15 sesquiterpene coumarins were isolated and purified from different species of *Ferula*. 50 µM of umbelliprenin, farensiferol B, farenciferol C and lehmferin were used. The Flow Cytometry results showed that intracellular accumulation of doxorubicin 123 significantly increased in MCF7/Adr cells when treated with sesquiterpene coumarins. Farnesiferol B, farnesiferol C and lehmferin had the most significant inhibitory effects on the P-glycoprotein pump (Kasaian *et al.*, 2015). In the previous review article, this issue has been addressed entitled *Reversal of multi-drug resistance* (Sattar and Iranshahi, 2017). The effect of the methanolic extract of *F. persica* var. *Persica* and *F. hezarlalehzarica* on $HepG_2$, A_{549}, HT_{29}, and MCF7 cancer cell lines and a normal MDBK cell line using MTT assay investigated by Hajimehdipoor *et al*. (2012). The results showed that among the studied fractions including hexane, chloroform, ethyl acetate, pure or 50% methanol, only chloroform and hexane components of these plants had cytotoxic effects up to 100 µg/mL, so that *F. persica* var. *Persica* with IC_{50} of 22.3-71.8 µg/mL was more toxic than that of *F. hezarlalehzarica* with IC_{50} of 76.7-105.3 µg/mL (Hajimehdipoor *et al.*, 2012).

Valiahdi *et al*. (2013) studied the cytotoxic activity of various fractions of *Ferula* species on ovarian carcinoma (CH_1), lung cancer (A_{549}), and melanoma (SK-MEL-28) cell lines. The results indicated a moderate cytotoxic activity of the studied compounds with IC_{50} values in the micromolar range. The highest activity against CH_1 and A_{549} lines was about conferon, while stylosin and tschimgine showed the most potent cytotoxicity against SK-MEL-28 (Valiahdi *et al.*, 2013). Aghbali *et al*. (2015) investigated the effect of the methanolic extract of *F. persica* on oral squamous cell carcinoma induced by 4-nitroquinoline-1-oxide (4-NQO) in male rats. The extract at doses of 50, 250, and 500 mg/kg was intraperitoneally administered twice a week for 14 weeks. The histopathological results of these animals' tongue tissue showed that the plant extract significantly reduced the severity of the histopathological lesions, especially squamous cell carcinoma and carcinoma *in situ* induced by 4-NQO at all doses (Aghbali *et al.*, 2015). It has been said that umbelliprenin induces apoptosis in Jurakt cells through affecting caspase pathways. Umbelliprenin activates intrinsic and extrinsic pathways of apoptosis with increasing caspase 9 and 8 proteins, respectively (Gholami *et al.*, 2013).

In this regard, it has been reported that umbelliprenin is able to protect against the spread and recurrence of malignant melanoma in humans with minimal side effects (Barthomeuf *et al.*, 2008). Also, the hydroalcoholic extracts of *F. persica* leaf, stem, and flower at doses of 50, 250, and 500 mg/kg were used, and the effect of the extracts on 4-NQO-induced oral squamous cell carcinoma was studied in male rats. In this regard, the blood level of Cyclooxygenase-2 was evaluated. This study showed that the plant could not reduce Cyclooxygenase-2 as a mechanism to fight squamous cell carcinoma and played no influential role in this field (Vosoughhosseini *et al.*, 2018). Cyclooxygenase-2 is an enzyme produced by epithelial cells that stimulated with growth factors, cytokines, and mitogens. It produces prostaglandins in response to inflammation, cell proliferation and differentiation, angiogenesis, and metastasis. Increased Cyclooxygenase-2 has been reported in a variety of tumors, including colon, lung, gall bladder, and hypopharynx (Gallo *et al.*, 2001; Shiotani et al., 2001; Peng *et al.*, 2002; Vered *et al.*, 2005; Arima et al., 2006; Kitakawaa *et al.*, 2006; Neville *et al.*, 2009).

Hoseinzadeh *et al*. (2020) evaluated the cytotoxic effect of *F. persica* gum essential oil on murine colon carcinoma (CT26) and Vero cell lines at 0.125×10^{-9} to 20 µl/mL and 0.125×10^{-9} to 80µl/mL concentrations for 24 hours by MTT assay respectively. The results showed that the essential oil has dose-dependent toxicity on CT26 with IC_{50}= 0.0010 µl/mL and on Vero cell lines with IC_{50}= 0.3247 µl/mL. Also, it was expressed that the essential oil induced apoptosis in both cell lines. This result was determined by the

staining of acridine orange/ethidium bromide (AO/EB) (Hosseinzadeh *et al.*, 2020).

It should be noted that *F. persica* extract or essential oil has been used for green synthesis of silver and gold nanoparticles. In this regard, in another study by the same authors (2020), cytotoxicity and apoptosis of gold nanoparticles synthesized by *F. persica* gum essential oil on CT26 and Vero cell lines were evaluated. AuNPs induced dose-dependent cytotoxicity with IC_{50} values of 0.0024 and 0.0307 mg/mL against CT26 and Vero cell lines, respectively. AuNPs induced apoptosis in both cell lines (Hosseinzadeh *et al.*, 2020). Also, in another recent study (2021), the cytotoxic activity of silver nanoparticles synthesized by *F. persica* extract was investigated using two cell lines, MCF-7 (breast cancer) and AGS (human gastric carcinoma). Antitumor activity of these nanoparticles against MCF-7 and AGS was determined with IC_{50} values of 21.28 and 11.07 µg/mL, respectively (Hashemi *et al.*, 2021).

6.2. Effect on Alzheimer's disease

Some coumarin compounds have demonstrated the inhibitory effects of acetylcholine esterase (Kim *et al.*, 2002; Phoopichayanun *et al.*, 2008; Zhou *et al.*, 2008). The *Ferula* is full of sesquiterpene. The study of Piazi *et al*. (2008) led to observations of coumarin compounds with potent inhibitory effects on acetylcholinesterase. This study showed that the impact of the herbal compounds were comparable to the standard anti-Alzheimer's drug "Donepezil" (Piazzi *et al.*, 2008). Shekarchi *et al*. (2013) studied the effect of the total extract of six *Ferula* species, including *F. hezarlalehzarica*, *F. hirtella*, *F. oopoda*, *F. ovina*, *F. persica* var. *Persica* and *F. szowitsiana* on acetylcholinesterase *in vitro*. The results showed that the chloroform fraction of *F. persica* var. *Persica* had acceptable acetylcholinesterase inhibitory effects (27.3%), and other extracts had minor inhibitory effects (Shekarchi *et al.*, 2013).

Karimi *et al*. (2010) studied the inhibitory effect of eight natural compounds of coumarin derivatives and terpenoids of *Ferula* species on human erythrocyte acetylcholinesterase. The compounds included aurapten, diversin, diversolide D, farnesiferol A, galbanic acid, tschimgine, umbelliferone, and umbelliprenin. Herniarin and 7-isopentenyloxy coumarin at 100 mM were also used against human acetylcholinesterase. The results showed that among the ten studied compounds, tschimgine was the most potent acetylcholinesterase inhibitor (63.5% inhibition). However, the inhibitory activity of none of the compounds was comparable to that of galantamine (86.4% inhibition) as the reference inhibitor. The esteric monoterpene tschimgine is used as a lead molecule to design anticholinesterase agents (Karimi *et al.*, 2010). The *in vitro* and *in vivo* findings showed that the natural components of some species of *Ferula*, i.e., umbelliferone and ferulic acid, were competitive acetylcholinesterase inhibitors.

In addition, among volatile components of some *Ferula* species, eugenol and limonene inhibit acetylcholinesterase (Kumar *et al.*, 2009). In addition to aurapten, prenylated coumarin has neuroprotective activity and a mild acetylcholinesterase inhibitory effect (Miyazawa *et al.*, 2001; Epifano *et al.*, 2008; Loizzo *et al.*, 2008).

6.3. The effect on sleeping time and morphine withdrawal syndrome

Vafaei *et al*. (2004) investigated the effect of *F. persica* extract on the modulation of withdrawal syndrome signs in morphine-dependent male albino mice. In this study, *F. persica* extract used at doses of 50, 100 and 200 mg/kg. The results showed that *F. persica* extract at different doses significantly modulated withdrawal syndrome signs only for weight loss and not for number of jumping in morphine-dependent mice (Vafaei *et al.*, 2004). Also, the effect of the hydroalcoholic extract of *F. persica* aerial parts on morphine withdrawal symptoms and sleeping time in mice was studiedby Jadidi *et al*. (2010). In this study, the extract at 50, 100, and 200 mg/kg was administered intraperitoneally in the morphine dependent mice, which the dependence had been induced by the Marshall method (Marshall and Grahame-Smith, 1994). The plant extract was injected to the animals half an hour before administration of naloxone. The results showed that the hydroalcoholic extract of *F. persica* had no effect on morphine withdrawal symptoms such as number of jumps and only decreased fecal excretion and diarrhea yet produced a hypnotic effect in a dose-dependent manner (Jadidi *et al.*, 2010).

6.4. Antiepileptic effects

Various species of *Ferula*, such as *F. asafoetida* and *F. gummosa* have been reported to have anticonvulsant effects (Sayyah *et al.*, 2002). Bagheri *et al*. (2010)

studied the anticonvulsant effects of methanolic extracts of *F. persica*, *F. badrakema* and *F. ovina* aerial parts (300 mg/kg) in mice. The results showed none of the extracts prevented pentylenetetrazole-induced seizure (Bagheri *et al.*, 2010).

Recently a double-blind, randomized, placebo-controlled trial, conducted to investigate the effect of *Dorema Ammoniacum* and *F. Persica* oleo-gum resins combination product on seizure control in epileptic patients. A total number of 162 individuals were screened, 58 were eligible, and were devided randomly into two groups (27: treatment and 31: control groups). The patients received drug/placebo three times a day for three months. Drug capsules contained 350 mg of *Dorema ammoniacum* oleo-gum resin and 150 mg of *F. Persica* oleo-gum resin. Placebo capsules were filled with 500 mg lactose powder. The results showed that seizure frequency did not reduce significantly in the treatment vs placebo group after one, two, and three months periods (Hesami *et al.*, 2022).

6.5. Analgesic and anti-inflammatory effects

Various studies have shown that coumarins produce analgesic effects (Leal *et al.*, 2000; Iranshahi *et al.*, 2009c; de Almeida Barros *et al.*, 2010; Iranshahi *et al.*, 2011). Umbelliprenin is chemically related to 7-hydroxy coumarins with analgesic, anti-inflammatory, and antipyretic activities *in vitro* and *in vivo* (de Almeida Barros *et al.*, 2010). Iranshahi *et al.* (2009) investigated the antioxidant, anti-inflammatory and lipoxygenase inhibitory activities of the umbelliprenin (the active ingredient of the Apiaceae family and the genus *Ferula*) in rats. The results showed that umbelliprenin had no significant antioxidant activity but a significant inhibitory effect against lipoxygenase with IC_{50} of 0.0725μM. In addition, this compound could significantly inhibit paw edema induced by Carrageenin by 39% (Iranshahi *et al.*, 2009c).

Hashemzaei *et al.* (2015) investigated the analgesic effects of umbelliprenin alone and in combination with morphine in albino mice. The results showed that a single dose of umbelliprenin (0.01 mM/kg) significantly reduced neuropathic pain. Umbelliprenin also enhanced the effect of morphine on neuropathic pain so that co-administration of morphine and umbelliprenin can be recommended instead of traditional analgesic therapies (Hashemzaei *et al.*, 2015). Umbellipreninhas a remarkable inhibitory activity on lipoxygenase (a key enzyme in inflammatory processes) with an IC_{50} of 0.0725 μM that is significant, when compared wiyh caffeic acid as the standard drug with an IC_{50} of 600 μM (Iranshahi *et al.*, 2009c).

It has been shown that intraperitoneal injection of umbelliprenin at a concentration of 0.01 mM significantly improves inflammation, comparable to Indomethacin (Iranshahi *et al.*, 2009c). In another recent study by Rabbani, the effect of hydroalcoholic extract of *F. persica* gum on rheumatoid arthritis induced by Freund's complete adjuvant was investigated in the rat knee joint. The extract was used at doses of 25, 50, and 70 mg/kg, and the results showed that rheumatoid factor levels significantly decreased in the groups taken the extract.This study also showed that *F. persica* extract at 70 mg/kg could completely regenerate cartilage along with obvious metachromasia, due to certain active ingredients, such as umbelliprenin in the *F. persica* gum (Rabbani *et al.*, 2018). The anti-inflammatory effect of umbelliprenin through inhibiting lipoxygenase and metalloproteases has been proven to prevent the degenerative process of rheumatoid arthritis (Iranshahi *et al.*, 2009c). Rheumatoid factor in patients with definite clinical symptoms is usually positive in the first six months. Rheumatoid factors are autoantibodies that react with immunoglobulin G (Van Schaardenburg *et al.*, 1993).

6.6. Antibacterial activity

The effects of aqueous, chloroform extracts, and active ingredient umbelliprenin of *F. persica* var. *persica* roots against many bacteria, including *Bacillus cereus*, *Bacillus subtilis*, *Citrobacter freundii*, *E. coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Serratia marcescens*, *Shigella dysenteriae*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus faecalis*, and *Pseudomonas aeruginosa* were evaluated by Shahverdi *et al.* (2005), using Disk Diffusion method. The results showed that the tested concentrations (0.5, 1, 2 and 4 mg/mL) of the aqueous extract have no antibacterial activity.

At the highest concentration (4 mg/mL), chloroform extract showed desirable antibacterial activity, especially against *S.epidermidis* and *E. coli*, and at none of the studied concentrations (0.5, 1, 2 & 4 mg/mL), was effective against other bacteria. Besides that, umbelliprenin, the most active ingredient of *F. persica*, at 500 μg/mL showed the most significant activity against *B. subtilis*, *B. cereus*, *E-coli*, *Klebsiella*

pneumoniae, *S. typhi*, *S. aureus*, *S. epidermidis* (Shahverdi *et al.*, 2005a).

Iranshahi *et al.* (2014) studied the effect of chloroform extract of *F. persica* var. *persica* root and its active ingredient, umbelliprenin, on the pigment production of *Serratia marcescens*, a causative agent of nosocomial infections that can be life-threatening (Haddy *et al.*, 1996; Hejazi and Falkiner, 1997). The results showed that neither umbelliprenin nor crude extract of *F. persica* could inhibit bacterial growth. At the same time, both effectively induced depigmentation zones on *S. marcescens* culture media and the bleaching effect of umbelliprenin was concentration-dependent, so the highest concentration used was 1.5 µmol, whereas a bleaching effect was observed at 0.6 µmol of umbelliprenin (Iranshahi *et al.*, 2014). After invertigating the inhibitory effect of umbelliprenin on pigment production in *Serratia marcescens*, Shahverdi *et al.* (2005) further studied the umbelliprenin bleaching effect, and its IC_{50} as 38 µM was calculated. In this study, the effect of other coumarins derived from *F. persica* root on *S. marcescens* depigmentation was evaluated as well. Neither of these compounds had a bleaching effect against the tested strain at a specific concentration. Comparison of the structure of other coumarins showed that the linear sesquiterpene part of the umbelliprenin structure was essential for the bleaching effect against *S. marcescens* (Shahverdi *et al.*, 2005b).

The effects of *F. persica* gum extract (125 and 250 mg/mL) and gold nanoparticles (12.5, 25, and 50 ppm) on *Pseudomonas aeruginosa* isolated from burn wounds have been investigated by agar well-diffusion and microdilution antimicrobial susceptibility tests. The results showed that the most significant inhibitory effect was obtained for 250 mg/mL of *F. persica* gum extract, that was equivalent to the inhibitory effect of ciprofloxacin as the reference drug. The MIC and MBC of the extract were reported to be 69.25 and 102.25 mg/mL, respectively (Nasrollahi Nejad *et al.*, 2017). Recently, the antibacterial activity of the silver nanoparticles synthesized by *F. persica* extract was evaluated against seven pathogenic bacteria. The MBC of newly synthesized nanoparticles was 62.5 µg/mL for *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterococcus faecalis*, 125 µg/mL for *Staphylococcus aureus* and 250 µg/mL for *Enterococcus faecalis* (Hashemi *et al.*, 2021).

6.7. Antigenotoxicity

Noroozi *et al.* (2008) investigated the effect of persicasulfide A (isolated from *F. persica* on hydrogen peroxide (H_2O_2)-induced DNA damage in lymphocytes of healthy male Wistar rats. The results showed a 50% reduction in DNA damage, compared with EC_{50} for ascorbic acid as the reference drug (1399.23 µM). It is argued that persicasulfide A prevents oxidative damage to DNA more effectively than ascorbic acid (Noroozi *et al.*, 2009). In another study, the effect of umbelliprenin on human lymphocyte DNA damage was evaluated by Soltani *et al.* (2009). The results showed that umbelliprenin caused a concentration-dependent increase in the protective activity against hydrogen peroxide-induced DNA damage (from 67.28% to 39.17%) (Soltani *et al.*, 2009).

6.8. Other pharmacological effects

Ghanbari *et al.* (2012) reported that the intravenous administration of aqueous extract of *F. persica* aerial parts at doses of 15, 30, and 60 mg/kg lowered blood pressure in healthy and hypertensive rats. However, treatment with this extract at 30 mg/kg in drinking water did not affect arterial blood pressure (Ghanbari *et al.*, 2012). Aqueous *F. persica* extract was investigated for inhibiting alpha-amylase *in vitro* and hypoglycemic function *in vivo* in normoglycemic and streptozotocin-induced hyperglycemic rats. The results showed no significant difference between the control and treatment groups (Hamdan and Afifi, 2004).

In another study by Ataee *et al.* (2020), the protective effect of the methanolic extract of *F. persica* aerial parts and root (62.5, 125, and 250 mg/kg bw) against hypoxia and its mortality in mice was evaluated by experimental models of asphyctic, haemic, and circulatory hypoxia. The results showed that the extract of aerial parts and root of *Ferula* at 62.5 and 125 mg/kg resulted in a survival time increase in asphyctic hypoxia, respectively. Regarding haemic hypoxia, aerial parts and root extracts showed the same effect at equal doses. Eventually, both extracts at 62.5 mg/kg showed proper protective effect and increased survival time in circulatory hypoxia. It was expressed that the presence of polyphenols in this plant may be a proposed mechanism for its anti-hypoxic activities (Ataee *et al.*, 2020).

Also, Mirkazem *et al.* (2021) indicated that methanolic or aqueous extracts of *F. persica* and

Nelumbo nucifera alone or combined in a ratio of 1:2 at 50 µg/mL reduce pancreatic lipase activity *in vitro* (Mirkazem *et al.*, 2021). The antifungal activity of aqueous and chloroform extracts of *F. persica* var. *Persica* roots were also evaluated by the disk diffusion method. The chloroform extract at the studied concentrations showed antifungal activity. The active ingredients of the extract identified by PTLC, including persicasulfide A and persicasulfide B, showed the most potent antifungal activity against filamentous fungi with MICs below 62.5 µg/mL (Mirjani *et al.*, 2005). The antileishmanial activity of silver nanoparticles synthesized by *F. persica* was studied in vitro, too. It was demonstrated that FpNPs could inhibit promastigotes and amastigotes with IC_{50} values of 23.14 µg/mL and 26.43 µg/mL, respectively (Hashemi *et al.*, 2021).

In a recent study (2022), the wound-healing effect of *F. persica* methanolic extract was investigated in male Wistar rats. Histological and stereological assessments showed that the extract ointment (%5w/w) could improve circular and linear wounds area after 9 and 17 days, respectively. In fact, after treatment duration, the fibroblast cells and collagen deposition increased, inflammatory cells decreased, and remarkable neovascularization was found in the extract group comparing negative and vehicle control groups. Expression of TNF-α was reduced, and TGF-β gene expression increased by the extract. Also, elevated cyclooxygenase-2 expression in control groups, improved in the extract group. It has been said that the high antioxidant content of this medicinal plant could have recovered the damaged tissue remarkably (Huang *et al.*, 2022).

7. Toxicological studies

In a recent study (2019), the oral toxicity of methanolic extract of *F. persica* was investigated in female mice. For acute toxicity, flower and leaf extracts were gavaged to mice at 5, 50, 300, and 2000 mg/kg doses, and their behavioral and appearance changes were monitored for 48 hours. Subsequently, observations were recorded for up to 14 days due to no noticeable difference. To evaluate sub-chronic toxicity, the mice were gavaged individually for 28 days in a single dose of 1000 mg/kg/d. The results showed that none of the mice showed any behavioral and appearance changes during the 48 hours and were observed to remain healthy for 14 days. This study showed that the LD_{50} of the extract was more than 2000 mg/kg, and no mortality was observed in mice.

Biochemical study of glucose, urea, creatinine, electrolytes including sodium and potassium, protein, albumin, liver enzymes including aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), bilirubin, the lipid profile including cholesterol and triglyceride was evaluated at the end of day 28. No significant change was observed in the control and treatment groups. Besides, in control and treatment groups, no significant differences were observed in hematologic factors, including red blood cells, white blood cells, hemoglobin, hematocrit, neutrophils, and lymphocytes. The histopathology of mice also showed no marked change in ovarian, uterine, kidney, liver, spleen, heart, and lung tissues (Soleimani Far *et al.*, 2019).

8. Pharmaceutical products

Due to the numerous active ingredients in *F. persica*, its various pharmacological effects, and its lack of toxicity, the plant can treat many disorders effectively. However, further research is still needed in this area, including investigating interactions of this plant with other herbs or medications and human studies (clinical trials). The present study can serve as a practical step towards optimizing the use of this plant in various disorders to maintain health and can provide an overview of the different valuable studies carried out on this plant.

9. Conclusion

Due to the numerous active ingredients in *F. persica*, its various pharmacological effects, and its lack of toxicity, the plant can treat many disorders effectively. However, further research is still needed in this area, including investigating interactions of this plant with other herbs or medications and human studies (clinical trials). The present study can serve as a practical step towards optimizing the use of this plant in various disorders to maintain health and can provide an overview of the different valuable studies carried out on this plant.

10. References

Abdallah, H.M., Al-Abd, A.M., El-Dine, R.S. and El-Halawany, A.M. 2015. P-glycoprotein inhibitors of natural origin as potential tumor chemo-sensitizers: A review. *Journal of Advanced Research*, 6(1): 45-62.

Afifi, F.U. and Abu-Irmaileh, B. 2000. Herbal medicine in Jordan with special emphasis on less commonly used medicinal. *Journal of Ethnopharmacology*, 72: 101-110.

Aghbali, A., Mostafazadeh, S., Mesgari Abbasi, M., Fotoohi, S., Abdollahi, B., Janani, M. and Moradzadeh Khiavi, M. 2015. The Protective effect of the methanolic extract of *Ferula persica* in rat tongue neoplasm (oral squamous cell carcinoma) induced by 4-Nitroquinoline-1-Oxide (4-NQO). *Iranian Red Crescent Medical Journal*, 18(12):e25710.

Ahvazi, M., Khalighi-Sigaroodi, F., Charkhchiyan, M.M., Mojab, F., Mozaffarian, V. and Zakeri, H. 2012. Introduction of medicinal plants species with the most traditional usage in Alamut region. *Iranian Journal of Pharmaceutical Research*, 11(1): 185-194.

Akhondzadeh, S. 2000. *Encyclopedia of Iranian medicinal plants.* Arjmand Press, Tehran, pp. 76-77 [In Persian].

Arima, Y., Nishigori, Ch., Takeuchi, T., Oka, Sh., Morimoto, K., Utani, A. and Miyachi, Y. 2006. 4-Nitroquinoline 1-oxide forms 8-hydroxydeoxyguanosine in human fibroblasts through reactive oxygen species. *Toxicological Sciences*, 91(2): 382–392.

Ataee, R., Hasani, H., Mohammadyan, M. and Ebrahimzadeh, M.A. 2020. Antihypoxic activities of aerial parts and roots of *Ferula persica* in mice. *Journal of Mazandaran University of Medical Sciences*, 30(189): 126-132 [In Persian].

Bagheri, S.M., Sahebkar, A.H., Gohari, A.R., Saeidnia, S., Malmir, M. and Iranshahi, M. 2010. Evaluation of cytotoxicity and anticonvulsant activity of some Iranian medicinal *Ferula* species. *Pharmaceutical Biology*, 48(3): 242-246.

Baradaran, A., Madihi, Y., Merrikhi, A., Rafieian-Kopaei, M. and Nasri H. 2013. Serum lipoprotein (a) in diabetic patients with various renal function not yet on dialysis. *Pakistan Journal of Medical Sciences*, 29(1):354-357.

Barthomeuf, C., Lim, S., Iranshahi, M. and Chollet, P. 2008. Umbelliprenin from *Ferula szowitsiana* inhibits the growth of human M4Beu metastatic pigmented malignant melanoma cells through cell-cycle arrest in G1 and induction of caspase-dependent apoptosis. *Phytomedicine*;15(1-2): 103–111.

de Almeida Barros, T.A., de Freitas, L.A.R., Filho, J.M.B., Nunes, X.P., Giulietti ,A.M., de Souza, G.E., Santos, R.R.D., Soares, M.B.P., and Villarreal, C.F. 2010. Antinociceptive and anti-inflammatory properties of 7- hydroxycoumarin in experimental animal models: potential therapeutic for the control of inflammatory chronic pain. *Journal of Pharmacy and Pharmacology*, 62(2):205-213.

Eigner, D. and Scholz, D. 1990. Das zauberb_chlein der gyani dolma. *Pharmazie in Unserer Zeit*, 19:141-152.

Epifano, F., Molinaro, G., Genovese, S., Ngomba, R.T., Nicoletti, F. and Curini, M. 2008. Neuroprotective effect of prenyloxycoumarins from edible vegetables. *Neuroscience Letters*, 443:57-60.

Fasihzadeh, S., Lorigooini, Z. and Jivad, N. 2016. Chemical constituents of *Allium stipitatum* regel (persian shallot) essential oil. *Der Pharmacia Lettre*, 8: 175–180.

Gallo, O., Franchi, A., Magnelli, L., Sardi, I., Vannacci, A., Boddit, V., Chiarugi, V. and Masini, E. 2001. Cyclooxygenase-2 pathway correlates with VEGF expression in head and neck cancer. Implication tumor angiogenesis and metastasis. *Neoplasia*, 3(1): 53-61.

Ghanbari, M., Zahedi Khorasani, M. and Vakili, A. 2012. Acute and chronic effects of *Ferula persica* on blood pressure of hypertensive rats and its possible mechanism of action. *Journal of Medicinal Plants*, 11(43):62-68.

Ghasemi, S. and Lorigooini, Z. 2016. A review of significant molecular mechanisms of fllavonoids in prevention of prostate cancer. *Journal of Chemical and Pharmaceutical Sciences*, 9:3388–3394.

Gholami, O., Jeddi-Tehrani, M., Iranshahi, M., Zarnani, A.H. and Ziai, S.A. 2013. Umbelliprenin from *Ferula szowitsiana* Activates both Intrinsic and Extrinsic Pathways of Apoptosis in Jurkat T-CLL cell line. *Iranian Journal of Pharmaceutical Research*, 12(3):371–376.

Haddy, R.I., Mann, B.L., Nadkarni, D.D., Cruz, R.F., El- shoff, D.J,, Buendia, F.C., Domers, T.A. and Oberheu, A.M. 1996. Nosocomial infection in the community hospital: severe infection due to *Serratia* species. *Journal of Family Practice*, 42:273-277.

Hajimehdipoor, H., Esmaeili, S., Ramezani, A., Jafari Anaraki, M. and Mosaddegh, M. 2012. The Cytotoxic Effects of *Ferula Persica* var. *Persica* and *Ferula Hezarlalehzarica* against HepG2, A549, HT29, MCF7 and MDBK Cell Lines. *Iranian Journal of Pharmaceutical science*, 8(2):113-117.

Hamdan, I.I. and Afifi, F.U. 2004. Studies on the in vitro and in vivo hypoglycemic activities of some medicinal plants used in treatment of diabetes in Jordanian traditional medicine. *Journal of Ethnopharmacology*, 93(1):117-121.

Hanafi-Bojd, M.Y., Iranshahi, M., Mosaffa, F., Tehrani, S.O., Kalalinia, F. and Behravan, J. 2011. Farnesiferol A from *Ferula persica* and galbanic acid from *Ferula szowitsiana* inhibit P-glycoprotein-mediated rhodamine efflux in breast cancer cell lines. *Planta Medica*, 77(14):1590–1593

Hashemi, Z., Mohammadyan, M., Naderi, Sh., Fakhar, M., Biparva, P., Akhtari, J. and Ebrahimzadeh, M.A. 2021. Green synthesis of silver nanoparticles using *Ferula persica* extract (Fp-NPs): Characterization, antibacterial, antileishmanial, and in vitro anticancer activities. *Materials Today Communications*, 27: 102264.

Hashemzaei, M., Sadeghi Bonjar, M.A., Tabrizian, K., Iranshahi, M., Iranshahy, M. and Rezaee, R. 2015. Evaluation of the analgesic effect of Umbelliprenin and Umbelliprenin-morphine co-administration on the acute, chronic and neuropathic pain. *Indian Journal of Pharmaceutical Education and Research*, 49(2):121-125.

Hejazi, A. and Falkiner, F.R. 1997. *Serratia marcescens*. *Journal of Medical Microbiology*, 46(11):903-912.

Hesami, O., Sistanizad, M., Lima, B.S., Abadi, T.H. and Ayazkhoo, L. 2022. Evaluating the efficacy and safety of *Dorema Ammoniacum* and *Ferula Persica* oleo-gum resins combination product on seizure control in epileptic patients: A randomized, double-blind, placebo-controlled study. *Journal of Complementary Medicine Research*, 13(1): 22-26.

Hoseinpour, F., Hashemnia, M., Cheraghi, H., Safikhani, R., Sheikhi, T. and Hasani, Z. 2021. Assessment of antioxidant and cutaneous wound healing effects of *Ornithogalum cuspidatum* hydroalcoholic extract in male Wistar rats. *Journal of Basic and Clinical Pathophysiology*, 9(1): 23-32.

Hoseinpour, F., Shomali, T. and Rafieian-Kopaei, M. 2017. Hypocholesterolemic activity of cornelian cherry (*Cornus mas L*.) fruits. *Journal of Complementary and Integrative Medicine*, 14(4): 2017-0007.

Hosseinzadeh, N., Shomali, T., Hosseinzadeh, S., Raouf Fard, F., Jalaei, J. and Fazeli, M. 2020. Cytotoxic activity of *Ferula persica* gum essential oil on murine colon carcinoma (CT26) and Vero cell lines. *Journal of Essential Oil Research*, 32(2):169-177.

Hosseinzadeh, N., Shomali, T., Hosseinzadeh, S., Raouf Fard, F., Pourmontaseri, M. and Fazeli, M. 2020. Green synthesis of gold nanoparticles by using *Ferula persica* Willd. gum essential oil: production, characterization and in vitro anticancer effects. *Journal of Pharmacy and Pharmacology*, 72(8):1013–1025.

Huang, L., Wang, M., Ebrahimzadeh, M.A., Jafari, A. and Jiang, K. 2022. Stereological and molecular studies on the effects of *Ferula persica* extract on wound healing in rats. *Veterinary Medicine and Science*, 8(1): 318-327.

Iranshahi, M., Amin, G. and Shafiee, A. 2004. A New Coumarin from *Ferula persica*. *Pharmaceutical Biology*, 42(6): 440–442.

Iranshahi, M., Amin, G., Amini, M. and Shafiee, A. 2003. Sulfur containing derivatives from *Ferula persica* var. *latisecta*. *Phytochemistry*, 63(8): 965–966.

Iranshahi, M., Amin, Gh., Sourmaghi, M.S., Shafiee, A. and Hadjiakhoondi, A. 2006. Sulphur-containing compounds in the essential oil of the root of *Ferula persica* Willd. var. *persica*. *Flavour and Fragrance Journal*, 21(2): 260-261.

Iranshahi, M., Askari, M., Sahebkar, A. and Hadjipavlou-Litina, D. 2009c. Evaluation of antioxidant, anti-inflammatory and lipoxygenase inhibitory activities of the prenylated coumarin umbelliprenin. *DARU. Journal of Pharmaceutical Sciences*,17(2): 99-103.

Iranshahi, M., Kalategi, F., Rezaee, R., Shahverdi, A.H., Ito, C., Furukawa, H., Tokuda, H. and Itoigawa, M. 2008b. Cancer chemopreventive activity of terpenoid coumarins from *Ferula* Species. *Planta Medica*, 74(2):147–150.

Iranshahi, M., Mahmoudi, M., Zamanai Taghizadeh Rabe, S.H. and Siadat, Z. 2011. Anti-inflammatory effect of Umbelliprenin from *Ferula szowitsiana* mediated by the inhibition of nitric oxide production by inflammatory macrophages. *Clinical Biochemistry*, 44(13):3-10.

Iranshahi, M., Noroozi, S., Behravan, J., Karimi, G. and Schneider, B. 2009a. Persicasulphide C, a new sulphur-containing derivative from *Ferula persica*. *Natural Product Research*, 23(17): 1584–1588.

Iranshahi, M., Sahebkar, A., Takasaki, M., Konoshima, T. and Tokuda, H. 2009b. Cancer chemopreventive activity of the prenylated coumarin, umbelliprenin, in vivo. *European Journal of Cancer Prevention*, 18(5): 412-415.

Iranshahi, M., Shahverdi, A.R., Mirjani, R., Amin, G., Shafiee, A. 2014. Umbelliprenin from *Ferula persica* roots inhibits the red pigment production in *Serratia marcescens*. *Zeitschrift für Naturforschung C*, 59 (7-8): 506-508.

Iranshahi. M., Mojarab, M., Sadeghian, H., Hanafi-Bojd, M.Y. and Schneider, B. 2008a. Polar secondary metabolites of *Ferula persica* roots. *Phytochemistry*, 69(2): 473–478.

Izadinia, J. 2019. Chemical composition of the essential oil obtained from leaf and flower of *Ferula persica* Willd.var. *Persica* by using GC and GC-MS. *Journal of Quantum Chemistry and Spectroscopy*, 31: 55-67 [In Persian].

Jadidi, M., Vafaei, A.A., Miladi-Gorji, H. and Babaei Saeidabadi, A.2010. Effect of *Ferula persica* L. extract on Morphine withdrawal symptoms and sleeping time in mice. *Journal of Medical Research*, 34(4): 225-230 [In Persian].

Jalili, A. and Jamzad, Z. 1999. Red Data Book of Iran: a preliminary survey of endemic, rare and endangered plant species of Iran. Research Institute of Forests and Rangelands, Tehran.

Javidnia, K., Miri, R., Kamalinejad, M. and Edraki, N. 2005. Chemical composition of *Ferula persica* Wild. Essential oil from Iran. *Flavour and Fragrance Journal*, 20(6): 605–606.

Kanani, M.R., Rahiminejad, M.R., Sonboli, A., Mozaffarian, V., Kazempour Osaloo, S. and Nejad Ebrahimi, S. 2011. Chemotaxonomic significance of the essential oils of 18 *Ferula* species (Apiaceae) from Iran. *Chemistry and Biodiversity*, 8(3): 503-517.

Karimi, Gh., Iranshahi, M., Hosseinalizadeh, F., Riahi, B., Sahebkar, AH. 2010. Screening of acetylcholinesterase inhibitory activity of terpenoid and coumarin derivatives from the genus *Ferula*. *Pharmacologyonline*, 1: 566-574.

Kasaian, J., Mosaffa, F., Behravan, J., Masullo, M., Piacente, S., Ghandadi, M. and Iranshahi, M. 2015. Reversal of P-glycoprotein-mediated multidrug resistance in MCF-7/Adr cancer cells by sesquiterpene coumarins. *Fitoterapia*, 103: 149-154.

Khorramizadeh, M.R., Esmail-Nazari, Z., Zarei-Ghaane, Z., Shakibaie, M., MollazadehMoghaddam, K., Iranshahi, M. and Shahverdi, A.R. 2010. Umbelliprenin-coated Fe_3O_4 magnetite nanoparticles: Antiproliferation evaluation on human Fibrosarcoma cell line (HT-1080). *Materials Science and Engineering C*, 30(7): 1038–1042.

Kim, D.K., Lim, J.P., Yang, J.H., Eom, D.O., Eun, J.S. and Leem, K.H. 2002. Acetylcholinesterase inhibitors from the roots of *Angelica dahurica*. *Archives of Pharmacal Research*, 25(6):856-859.

Kitakawaa, D., Cabrala, L.A.G., Marquesb, M.E.A., Salvadorib, D.M.F., Ribeiro, D.A. 2006. Medium-term tongue carcinogenesis assays: A comparative study between 4-nitroquinoline 1- oxide (4NQO)-induced rat and dimethylbenzanthracene (DMBA)-induced hamster carcinogenesis. *Journal of Experimental Animal Science*, 43(3): 219–227.

Krishna, R. and Mayer, L.D. 2000. Multidrug resistance (MDR) in cancer. Mechanisms, reversal using modulators of MDR and the role of MDR modulators in influencing the pharmacokinetics of anticancer drugs. *European Journal of Pharmaceutical Sciences*, 11(4): 265–283.

Kumar, P., Singh, V.K. and Singh, D.K. 2009. Kinetics of enzyme inhibition by active molluscicidal agents ferulic acid, umbelliferone, eugenol and limonene in the nervous tissue of snail lymnaea acuminata. *Phytotherapy Research*, 23:172-177.

Leal, L.K.A.M., Ferreira, A.A.G., Bezerra, G.A., Matos, F.J.A. and Viana, G.S.B. 2000. Antinociceptive, anti-inflammatory and bronchodilator activities of Brazilian medicinal plants containing coumarin: a comparative study. *Journal of Ethnopharmacology*, 70(2): 151-159.

Loizzo, M.R., Tundis, R., Menichini, F. and Menichini, F. 2008. Natural products and their derivatives as cholinesterase inhibitors in the treatment of neurodegenrative disorders: an update. *Current Medicinal Chemistry*, 15(12): 1209-1228.

Lorigooini, Z., Ayatollahi, S.A., Amidi, S. and Kobarfard, F. 2015. Evaluation of anti-platelet aggregation effect of some *Allium* species. *Iranian Journal of Pharmaceutical Research*, 14(4): 1225-1231.

Lorigooini, Z., Kobarfard, F. and Ayatollahi, S.A. 2014. Anti-platelet aggregation assay and chemical composition of essential oil from *Allium atroviolaceum* Boiss growing in Iran. *International Journal of Biosciences*, 5(2): 151-156.

Mandegary, A., Sayyah, M., Heidari, M.R. 2004. Antinociceptive and anti-inflammatory activity of the seed and root extracts of *Ferula Gummosa* Boiss in mice and rats. *Daru*, 12(2): 58-62.

Marshall, L. and Grahame-Smith, D.G. 1994. Evidence against a role of brain 5-HT in the development of physical dependence upon morphine in mice. *Journal of Pharmacology and Experimental Therapeutics*, 197(3): 63.

Mirheidar, H. 2003. Plants Learnings. vol. 6. 5th ed. Daftare Nashre Farhange Eslami, Tehran, pp. 364 [In Persian].

Mirhoseini, M., Baradaran, A. and Rafieian-Kopaei, M. 2013. Medicinal plants, diabetes mellitus and urgent needs. *Journal of HerbMed Pharmacology*, 2(2): 53-54.

Mirjani, R., Shahverdi, A.R., Iranshahi, M., Amin, G. and Shafiee, A. 2005. Identification of Antifungal Compounds from *Ferula persica*. var. *persica*. *Pharmaceutical Biology*, 43(4): 293-295.

Mirkazem, M., Sahmani, M., Aali, E., GhorbaniNohooji, M., Javadi, A. and Goodarzvand Chegini, K. 2021. Inhibitory Effect of *Ferula persica*, *Ginkgo biloba*, *Nelumbo nucifera*, and Dicyclomine on the Activity of Pancreatic Lipase. *Journal of Mazandaran University Medical Sciences*, 31(203): 50-60 [In Persian].

Miyazawa, M., Tougo, H. and Ishihara, M. 2001. Inhibition of acetylcholinesterase activity by essential oil from *Citrus paradisii*. *Natural Product Letters*, 15: 205-210.

Mozaffarian, V. 1983. The Family of Umbelliferae in Iran: Keys and Distribution. Research Institute of Forests and Rangelands Press, Tehran, pp. 114-116.

Mozaffarian, V. 1998. *A Dictionary of Iranian Plant Names*. Farhang-e Moaser Publication, Tehran, [In Persian].

Mozaffarian, V. 2004. *Taxonomy of Plants (Volume 1 and 2)*. Amir Kabir Publication, Tehran, [In Persian].

Musto, C.J. 2009. The Ancient and Medieval Pharmaceutical Treatments for Arthritis, Gout, and Sciatica [dissertation]. Raleigh, North Carolina State University, 65.

Nasri, H., Sahinfard, N., Rafieian, M., Rafieian, S., Shirzad, M. and Rafieian-kopaei, M. 2013. Effects of *Allium sativum* on liver enzymes and atherosclerotic risk factors. *Journal of HerbMed Pharmacology*, 2(2): 23-28.

Nasrollahi Nejad, B., Bamzadeh, Z. and Hejazi, S.H. 2017. Antimicrobial Effects of *Ferula persica* Gum Extract and Gold Nanoparticles on Pseudomonas aeruginosa. *Avicenna Journal Of Clinical Microbiology and Infection*, 4:36646. Neville, B., Damm, D.D., Allen, C. and Chi, A. 2009. Oral and maxillofacial pathology, 3rd ed, Saunders co, USA, pp. 409- 418.

Noroozi, S., Mosaffa, F., Soltani, F., Iranshahi, M., Karimi, G., Malekaneh, M., Haghighi, F. and Behravan J. 2009. Antigenotoxic effects of the disulfide compound persicasulfide A (PSA) on rat lymphocytes exposed to oxidative stress. *Planta Medica*, 75(1): 32-36.

Peng, J.P., Su, C.Y., Chang, H.C., Chai, C.Y., and Hung, W.C. 2002. Overexpression of cyclooxygenase 2 in squamous cell carcinomaof the hypopharynx. *Human Pathology*, 33(1): 100-104.

Phoopichayanun, C., Phuwapraisirisan, P., TipPyang, S. and Jongaramruong, J. 2008. Complete NMR assignment and absolute configuration of feronielloside, a new acetylcholinesterase inhibitor from *Feroniella lucida*. *Natural Product Research*, 22(15): 1297 -1303.

Piazzi, L., Cavalli, A., Colizzi, F., Belluti, F., Bartolini, M., Mancini, F., Recanatini, M., Andrisano, V. and Rampa, A. 2008. Multi-target-directed coumarin derivatives: hAChE and BACE1 inhibitors as potential anti-alzheimer compounds. *Bioorganic and Medicinal Chemistry Letters,*18(1): 423-426.

Rabbani, N., Tehranipour, M., Mahdavi Shahri, N. 2018. Effect of hydroalcoholic extract of *Ferula persica* resin on induced rheumatoid arthritis by Freund's complete adjuvant in rat. *Journal of Gorgan University Medical Sciences*, 20(3):24-30 [In Persian].

Rabiei, Z., Bigdeli, M. and Lorigooini, Z. 2015. A review of medicinal herbs with antioxidant properties in the treatment of cerebral ischemia and reperfusion.

Journal of Babol University of Medical Sciences, 17:45–76.

Rabiei, Z., Rafieian-kopaei, M., Heidarian, E., Saghaei, E. and Mokhtari, S. 2014. *Effects of Zizyphus jujube* extract on memory and learning impairment induced by bilateral electric lesions of the nucleus basalis of meynert in rat. *Neurochemical Research*, 39: 353-360.

Razavi, S.M. and Janani, M. 2015. A new ester coumarin from *Ferula Persica* wild, indigenous to Iran. *Natural Product Reports*, 29(8): 717-721.

Rezazadeh, S., Yazdani, D. and Shahnazi, S. 2003. Chemical composition of essential oil of *Ferulago angulata* Boiss. inflorescence from west of Iran. *Journal of Medicinal Plants*, 2(7): 49–52.

Sahebkar, A.H. and Iranshahi, M. 2010. Biological activities of essential oils from the genus *Ferula* (Apiaceae). *Asian Biomedicine*, 4(6): 835-847.

Samsam shariat, S.H. 2007. Collection of medicinal herbs. 2nd ed. Mani publications, Isfahan, [In Persian].

Sattar, Z. and Iranshahi, M. 2017. Phytochemistry and pharmacology of *Ferula persica* Boiss.: A review. *Iranian Journal of Basic Medical Sciences*, 20(1): 1-8.

Sayyah, M., Mandgary, A. and Kamalinejad, M. 2002. Evaluation of the anticonvulsant activity of the seed acetone extract of *Ferula gummosa* Boiss. against seizures induced by pentylenetetrazole and electroconvulsive shock in mice. *Journal of Ethnopharmacology*, 82(2-3):105–109.

Shahverdi, A.R., Iranshahi, M., Mirjani, R., Jamalifar, H., Amin, G. and Shafiee, A. 2005a. Bioassay-Guided isolation and identification of an antibacterial compound from *Ferula persica* var. *persica* roots. *DARU, Journal of Pharmaceutical Sciences*, 13(1):17-19.

Shahverdi, A.R., Mirjani, R., Amin, G., Shafiee, A. and Iranshahi, M. 2005b. Bleaching of *Serratia marcescens* by some coumarins: A spectrophotometric study. *Journal of Basic Microbiology*, 45(6):470–474.

Shahverdi, A.R., Saadat, F., Khorramizadeh, M.R., Iranshahi, M. and Khoshayand, M.R. 2006. Two matrix metalloproteinases inhibitors from *Ferula persica* var. *persica*. *Phytomedicine*, 13(9-10):712-717.

Shekarchi, M., Hajimehdipour, H., Naghibi, F., Ara, L., Moazzeni Zahan, H. 2013. Investigation of Acetylcholin esterase inhibitory activity of extract of some *Ferula* species. *Journal of Medicinal plants*, 2(46): 106-112 [In Persian].

Shiotani, H., Denda, A., Yamamoto, K., Kitayama, W., Endoh, T., Sasaki, Y., Tsutsumi, M., Sugimura, M. and Konishi, Y. 2001. Increased expression of cyclooxygenase-2 protein in 4-nitroquinoline-1-oxideinduced rat tongue carcinomas and chemopreventive efficacy of a specific inhibitor, nimesulide. *Cancer Research*, 61(4): 1451-1456.

Shirzad, H., Kiani, M. and Shirzad, M. 2013. Impacts of tomato extract on the mice fibrosarcoma cells. *Journal of HerbMed Pharmacology*, 2(1): 13-16.

Shirzad, H., Taji, F. and Rafieian-Kopaei, M. 2011. Correlation between antioxidant activity of garlic extracts and WEHI-164 fibrosarcoma tumor growth in BALB/c mice. *Journal of Medicinal Food*, 14(9): 969-974.

Soleimani Far, M., Mojab, F. and Arbabi Bidgoli, S. 2019. Acute and subchronic toxicity assessment of aerial parts of *Ferula persica* in female mice. *Journal of medicinal plants*, 18(69): 47-58 [In Persian].

Soltani, F., Mosaffa, F., Iranshahi, M., Karimi, G., Malekaneh, M., Haghighi, F. and Behravan, J. 2009. Evaluation of antigenotoxicity effects of umbelliprenin on human peripheral lymphocytes exposed to oxidative stress. *Cell Biology and Toxicology*, 25(3): 291-296.

Trease G.E. and Evans, W.C. 1989. Pharmacognosy. 13th ed. Bailliere Tindall, London, pp. 205-206.

Vafaei, A.A., Sajadi, A.A., Taherian, A.A., Emami Abarghoi, M., Miladi-Gorji, H. and Jarrahi, M. 2004. The effect of *Ferula persica* on modulation of withdrawal syndrome sign in morphine-dependent mice. *Iranian Journal of Pharmaceutical Research*, 3(1):72-78.

Valiahdi, S.M., Iranshahi, M. and Sahebkar, A.H. 2013.Cytotoxic activities of phytochemicals from *Ferula* species. *DARU,Journal of Pharmaceutical Sciences*, 21(39):1-7.

Van Schaardenburg, D., Lagaay, A.M., Otten, H.G. and Breedveld, F.C. 1993. The relation between class-specific serum rheumatoid factors and age in the general population. *British Journal of Rheumatology*, 32(7): 546-549.

Vered, M., Yarom, N. and Dayan, D. 2005.4NQO oral carcinogenesis: animal models, molecular markers and future expectations. *Oral Oncology*, 41(4): 337–339.

Vosoughhosseini, S., Aghbali, A., Emamverdizadeh, P., Razbani, M., Mesgari, M. and Barzegar, A. 2018. Effect of *Ferula persica* plant methanol extract on the level of Cox-2 in induced squamous cell carcinoma (SCC) in rat tongue. *Journal of Dental Research Dental Clinics Dental Prospects*, 12(2): 91-96.

Zargari, A. 1988. Medicinal plants. 4th ed. Tehran University Publication, Tehran, pp. 592-602 [In Persian].

Zhou, X., Wang, X.B., Wang, T. and Kong, L.Y. 2008. Design, synthesis and acetylcholinesterase inhibitory activity of novel coumarin analogues. *Bioorganic and Medicinal Chemistry*, 16(17): 8011-8021.