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Review Article

Anticancer Effects of *Ferula Assafoetida* and its Main Components

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ABSTRACT

In the folk medicine, numerous plants have been used for treatment of various disorders. Natural products play a critical role in prevention and therapy of several diseases. *Ferula assafoetida (F. assafoetida),* was used traditionally for dietary, food preservative, additive, spice and various medicinal purposes. The aim of this study was to consider the anticancer effects of *F. assafoetida* and main component on different studies. The databases such as, PubMed, Web of Science, Google Scholar, Scopus, and IranMedex were considered for searching of keywords. anticancer effects of *F. assafoetida* and its components including; improved the antioxidant level and reversed remarkably the induced ornithine decarboxylase activity and DNA synthesis, inhibition of VEGF-induced proliferation, VEGF -induced angiogenesis, reduced CD34 microvessel density index and Ki-67 proliferative index, inhibition of androgen receptor abundance and signaling and anti-proliferative actions on the cancer cells.

Keywords: *Ferula assafoetida*, Galbanic acid, Anticancer effects, Umbelliprenin

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Ferula assafoetida (Asafoetida) belongs to the Apiaceae family with approximately 130 species distributed throughout the Mediterranean and Central Asia. Oleogum resin obtained from the exudates of the living underground rhizome or tap roots of the plant (1). Asafoetida used in traditional medicine and as a spice in different foods in different countries (1).

F. assafoetida is a wild native plant in Iran and its gum extract has been used in Iranian traditional medicine for abdominal pain, constipation and diarrhea treatment (1). Leaves of *F. assafoetida* possess anthelmintic, carminative and diaphoretic properties. Stem of plant is used as brain and liver tonic, root as antipyretic (2). Asafoetida is used for treatment of several disorders in traditional

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medicine including epilepsy, asthma, stomach-ache, intestinal parasites, weak digestion and influenza (3). It has been also reported that oleo-gum resin of Asafoetida possess sedative, expectorant, analgesic, antiperiodic, ant-diabetic, anti-spasmodic, anti-inflammatory, contraceptive and anti-epileptic effects (4). Relaxant effects of Asafoetida on muscarinic receptors and possible mechanisms for functional antagonistic of guinea-pig tracheal smooth muscle have been studied (5, 6). The possible relaxant effect of Asafoetida on smooth muscles and its possible mechanisms have been reviewed (7). In pharmacological and biological studies, the ole-gum- resin of Asafoetida have been revealed to have antioxidant, antiviral, antifungal, anti- diabetic, molluscicidal, antispasmodic and antihypertensive (1). Acute and sub-chronic toxicity of Asafoetida was evaluated and the results indicated that single oral administration (500 mg/kg) and repeated doses (250 mg/kg) for 28 days of this plant did not induce mortality and obvious toxicological signs in rats (8). Oleo gum resin of Asafoetida can enhance regeneration and re-myelination and decrease the rat of lymphocyte infiltration in the neuropathic tissue in mice; therefore it acts as a neuroprotective and nerve simulative agent in peripheral neuropathy (9). Asafoetida resin can potentially inhibit monoamine oxidase B (MAO-B) and it can be used in the therapy of neurodegenerative diseases such as Parkinson's and Alzheimer's diseases (10). Meanwhile, Asafoetida has been reported to have acetylcholinestrase (AChE) inhibiting property in in vitro assay and in vivo on snail nervous system and researchers have proposed that the its memory increasing effect could be attributed to inhibitory effect of this plant on AChE in the rat brain (11). In behavioural models, the extract of plant dose-dependently improved memory in rats. In another behavioural

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model, the extract of Asafoetida ameliorated memory (12). In herbal medicine, the organs of plant such as: leaves, stems, roots, flowers, fruits and seeds were used as alternative and complementary therapy (13). Herbal products contain of complex active components or phytochemicals like flavonoids, alkaloids and isoprenoids. Therefore, it is frequently difficult to determine which component(s) of the herb(s) has more biological activity (14, 15). In the present review study, it was aimed to highlight the anticancer effects of Asafoetida and maine component on different studies.

Methods

The keywords including "Anticancer" or "Antitumor" and " *Ferula assafoetida*", "*Ferula components*," and "galbanic acid" were searched in the databases such as, PubMed, Web of Science, Google Scholar, Scopus, and IranMedex.

Constituents

Iranian Ferula assa-foetida oil, E-1-propyl sec-butyl disulfide is a major component (16) and 25 compounds were identified in the hydrodistilled oil. E-1-propenyl sec-butyl disulfide (40.0%) and germacrene B (7.8%) are the major components of Ferula assa-foetida. therefore, only two components constituted more than 70% of the oiby by using supercritical carbon dioxide under optimum conditions, l. The extraction yield, based on hydrodistillation (16). Ferula assa-foetida also contains a number of bioactive compounds, including galbanic acid (17).

The effects of *F. assafoetida*

Administration of *F. assafoetida* by oral gavage (100 mg/kg) on female BALB/c mice induced breast cancer with 4T1 cells (1×10^5 4T1 cells/0.1 ml of phosphate buffer solution) showed that treatment with *F. assafoetida* was effective in decreasing the tumor weight and tumor volume in treated mice. *F. assafoetida* d\ecreased lung, liver and kidney metastasis and also increased areas of necrosis in the tumor tissue. Body weight

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significantly increased in treated mice against control (18)

F. assafoetida extract inhibited two stage chemical carcinogenesis induced by croton oil and 7,12-dimethyl benzanthracene on mice skin with considerable reduction in papiloma formation in mice. *F. assafoetida* also increase the percentage of life span in these mice by 52.9% (19). Saleem et al[23] the potential of antioxidant and anticarcinogenic activity of asafoetida in Swiss albino mice were investigated. *F. assafoetida* improved the antioxidant level and reversed remarkably the induced ornithine decarboxylase activity and DNA synthesis. *F. assafoetida* can be an effective agent and capable of alleviating cutaneous carcinogenesis in the pretreatment of animals (20). The influences of *F. assafoetida* on the mammary epithelial tissue differentiation, hepatic drug metabolizing enzymes, antioxidant outlines and N-methyl-N-nitrosourea-induced mammary carcinogenesis in Sprague–Dawley rats was investigated. *F. assafoetida* significantly decreased tumor multiplicity after treatment and also reduced the number of terminal end buds during mammary gland differentiation (21).

F. assafoetida supplementation attenuates 1,2-dimethylhydrazine induced deleterious effects in of rats. The dose of *F. assafoetida* (10 mg/100 g) exhibited more prominent effect as it continuously influenced all the tested biochemical parameters, which can be used as a promising chemopreventive agent against colon carcinogenesis (22).

The effects of *F. asafoetida* component

Umbelliprenin is a member of prenylated coumarins that present in Ferula species, which its chemoprevention activity on the cancer was reported (23). The protective activities of umbelliprenin on the human lymphocytes DNA lesions were tested. Umbelliprenin exhibited a concentration-dependent increase in protection activity against DNA damage induced by 25 μM H_2O_2 (from 67.28% to 39.17%) (24).

Galbanic acid (GA) is a biologically active

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sesquiterpene coumarin from Ferula species. GA decreased androgen receptor (AR) abundance and signaling and induced G1 arrest in prostate cancer cells. AR plays an important role in the progression of castration-resistant prostate cancer, which is relatively resistant to current chemotherapeutic agents. GA has been demonstrated to exert anti-androgen and antineoplastic activities. GA also downregulated AR protein abundance and signaling in LNCaP cells through promoting proteosomal degradation, which is a distinct mechanism from AR antagonists including bicalutamide. In addition, GA induced G1 arrest in association with an inhibition of cyclin/CDK4/6/ RB/E2F pathway (25).

The inhibitory effects of galbanic acid (GA) on Hypoxia Inducible Factor-1 (HIF-1) activation during hypoxia and normoxia were investigate. MTT survival and Annexin V assays were used to evaluate GA cytotoxicity and apoptosis in treated cells showed that GA decreased the *in vitro* growth of OVCAR-3 human epithelial carcinoma cells with an IC_{50} of approximately as dose- and time-dependently. The early/late apoptosis in GA treated cells were revealed following phosphatidylserine of outer leaflet of the plasma membrane. GA also down-regulates HIF-1α and HIF-1β mRNA expression in both hypoxia and normoxia. GA did not inhibit *Akt* and *EGFR* mRNA expression, yet protein degradation investigation showed that GA shortened the half-life of EGFR through decreasing its stability with a decrease of nearly 2 and 3 h in A549 and OVCAR-3 cell lines, respectively. In addition, under expressed in GA treated cells downstream genes including *Eno 1* and *GluT-1*, are contributed in glycolysis, in hypoxia (26).

GA significantly decreased vascular endothelial growth factor (VEGF)-induced proliferation and inhibited VEGF-induced migration and tube formation of human umbilical vein endothelial cell (HUVEC). 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. GA also decreased Lewis lung cancer (LLC) cell proliferation with an apparent G2/M arrest, but did not induce apoptosis. *In addition,* Galbanic acid given by daily *i.p.* injection (1 mg/kg) inhibited LLC-induced angiogenesis in an intradermal inoculation model and inhibited the growth of *s.c.* inoculated LLC allograft in syngenic mice. Tumors treated with GA decreased CD34 microvessel density index and Ki-67 proliferative in immunohistochemistry assay (17).

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Conclusion

F. assafoetida gum has been used for various purpose in traditional medicine. The anticancer effects of *F. asssafoetida* and its components on different types of cancer such as *in vitro* and *in vivo* have been shown. The different mechanisms of anticancer effects of *F. assafoetida* and its components including; improved the antioxidant level and reversed remarkably the induced ornithine decarboxylase activity and DNA synthesis, decreased phosphorylation of MAPK, inhibition of VEGF-induced proliferation, VEGF-induced angiogenesis, reduced CD34 microvessel density index and Ki-67 proliferative index, inhibition of androgen receptor abundance and signaling and anti-proliferative actions on the cancer cells.