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MINIREVIEWS

Anticancer potential of *Ferula assa-foetida* and its constituents, a powerful plant for cancer therapy

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Abstract

Cancer is one of the main challenges of the health system around the world. This disease is increasing in developing countries and imposes heavy costs on patients and governments. On the other hand, despite various drugs, the death rate among cancer patients is still high and the current treatments have many harmful effects. In the traditional medicine of different countries, there are many medicinal plants that can be effective in the treatment of cancer. Ferula plants are traditionally used as spices and food or for medicinal purposes. *Ferula assa-foetida* is one of the famous plants of this genus, which has been used for the treatment of various diseases since ancient times. Among the main compounds of this plant, we can mention monoterpenes, sulfide compounds and polyphenols, which can show different therapeutic effects. This article has been compiled with the aim of collecting evidence and articles related to the anti-cancer effects of extracts, derived compounds, essential oils and nanoparticles containing *Ferula assa-foetida*. This review article was prepared by searching the terms *Ferula assa-foetida* and cancer, and relevant information was collected through searching electronic databases such as ISI Web of Knowledge, PubMed, and Google Scholar. Fortunately, the results of this review showed that relatively comprehensive studies have been conducted in this field and shown that *Ferula assa-foetida* can be very promising in the treatment of cancer.

Key Words: *Ferula assa-foetida*; Anticancer; Essential oil; Isolated components; Nano particle; Extract

Core Tip: Finding new anti-cancer compounds is an important necessity in the treatment or prevention of this disease. *Ferula assa-foetida* has useful compounds for the prevention and treatment of cancer, which can be used in making new compounds. These compounds include sulphide compounds, flavonoids and terpene coumarins, which with new methods such as making emulsions and nanoparticles from these compounds can be of great help in reducing the costs of cancer patients and their life expectancy.

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INTRODUCTION

Today, one of the main problems of the health community is cancer, which is currently known as the second leading cause of death in the world. The most common cancers are breast and lung cancer worldwide, accounting for 12.5% and 12.2% of all newly diagnosed cases, respectively[1]. Common treatments include radiotherapy and chemotherapy that stop the cell cycle through apoptosis or non-apoptosis mechanisms such as necrosis[2]. These therapies have a variety of side effects, including damage to healthy cells. Medicinal plants have therapeutic value due to their biologically active compounds such as terpenes, coumarins, phenolic and alkaloids[3]. These natural compounds have shown promising insight into the treatment and prevention of cancer by restricting the division of tumor cells or inducing apoptosis with the advantage to reduce side effects[4]. The genus Ferula includes 170 different species that are distributed all over the world and this genus belongs to the Apiaceae (Umbelliferae) family[5]. *Ferula assa-foetida*, one of the famous species of Ferula that is used in Iranian traditional medicine for the treatment of digestive diseases, nervous problems and some reproductive system disorders such as decreased libido[6]. Asafoetida or Anghouzeh (Traditional name in Persian), is an oleo gum resin which obtained from the root of *Ferula assa-foetida* and traditionally used as anthelmintic, anticonvulsant, sexual aphrodisiac and analgesic agent[7]. New scientific reports have shown that asafoetida has antifungal[8], antidiabetic[9], antiinflammatory[10], antimutagenic[11] antidementia[12], anticonvulsant[13], antiviral[14], anti-cancer[15] and relaxant[16] activities and also has preventive effect against cuprizone induced demyelination[17]. There is not enough information available about the dosage and toxicity of asafoetida, but it is recommended not to consume more than 0.2 g per day[18], and it has also been shown that long-term and high-dose administration (200 mg and above) causes liver damage[19]. The main compounds that have been identified in the *Ferula assa-foetida* include glycoside compounds, various terpenoid, coumarin derivatives, and sulfide compounds[20,21] which have been shown to have anti-cancer potential (Figures 1 and 2).

Some compounds isolated from *Ferula assa-foetida* have also been shown to have various pharmacological properties. For example, Ferulic acid is one of these compounds that has antioxidant and neuroprotective properties[22]. Umbelliferon is a coumarin compound that has antioxidant and antidiabetic as well as antitumor effects[23]. In recent years, many studies have been conducted on the anti-cancer effects of Ferula. The members of this genus have shown high anti-cancer potential, which can provide a good basis for finding new anti-cancer agents. Our focus on published studies on the impact of different extracts and compounds isolated from *Ferula assa-foetida* as anticancer agents. Due to the increase in cancer patients and significant findings on the anticancer effects of *Ferula assa-foetida*, this article is designed for help to researchers finding new anticancer compounds.

METHOD

This review article was prepared by searching the terms of *Ferula assa-foetida* and cancer. Information about *Ferula assa-foetida* and its anticancer effect was collected on electronic databases including ISI Web of Knowledge, Medline/PubMed, ScienceDirect, Embase, Scopus, Biological Abstract, Chemical Abstract and Google Scholar. To make the research easier to understand, the article is divided into different sections, including the anti-cancer effects of nanoparticles containing *Ferula assa-foetida*, essential oils, extracts, isolated compounds from *Ferula assa-foetida*, and preclinical and experimental studies (Table 1).

Table 1 An overview of anticancer effect of different parts of *Ferula assa-foetida*

	Type/name	Cell line	Effects	Ref.
Nano particle	Silver nanoparticles and asafoetida ethanol extracts	L6 cancer cell line	IC50 was calculated 1 μg/mL	Subramaniam *et al* [25], 2021
	Nano emulsion containing *Ferula assa-foetida* seed essential oil	MCF7 and A2058 cell line	Increased BAX and decreased BCL2 expression. IC50 = 64 μg/mL for MCF7 and 201 μg/mL for A2058. Also, decreased VEGF at 32 μg/mL and VEGFR at 128 μg/mL	Azani *et al*[26], 2021
	Lipid nanoparticles containing *Ferula assa foetida* seed oil	NT-2 human cancer stem cells	IC50 = 115.4 μg/mL and the number of blood vessels reduced at 250, 500, and 1000 μg/mL	Sadat Khadem *et al* [27], 2021
	Silver anoparticles (AgNPs) with aqueous extract of asafoetida	MCF-7	IC50 was calculated 2 μg/mL	Devanesan *et al*[28], 2020
	Zinc nanoparticles containing *Ferula assa-foetida* extract	MCF7, MDA-MB231 and HT-29	IC50 was 23, 41.26 and 143 μg/mL after 72 h	Boskabadi *et al*[29], 2020
	Ferula assa foetida essential oil on PLGA nanoparticles	HepG2 and A2780	Inhibited HepG2 and A2780 with an IC50 of 57 μg/mL and 106.7 respectively. Reduction of vascular parametric factors at 125 μg/mL	Mokhtareeizadeh *et al*[30], 2021
Essential oil	(-)-E-2-butylpropenyl disulfide, (-)-Z-2-butylpropenyl disulfide, (-)-1-(methylthio) propyl (E)-1 -Propenyl disulfide, and (-)-1-(methylthio) propyl (Z)-1-propenyl disulfide	SKOV3 (ovary) and A549 (lung) cancer cell lines	Trisulfide showed better activity against A549 and SKOV3 cell lines compared to disulfides	Yatham *et al*[31], 2021
	Seed of *Ferula assa foetida* essential oil	AGS gastric cancer cells	Inhibitory effect on AGS gastric cancer cells was near 100% at 10 μl/mL after 72 h incubation	Bagheri *et al*[32], 2020
	Asafoetida essential oil	HepG2 and SK-Hep1	IC50 for HepG2 and SK-Hep1 was 7.21 μg/mL and 8.0 μg/mL respectively	Verma *et al*[33], 2019
	Essential oils asafoetida and	T98G and HCT116	IC50 value for HCT116 was 5.96 μg/mL and for T98G was 4.49 μg/mL	Pavela *et al*[34], 2020
	Essential oil of asafoetida	MCF7 cells	Decreased the viability of MCF7 cells in a time and concentration-dependent manner	Bagheri *et al*[35], 2020
Isolated components	Ferulic acid	MDA-MB-231	Combination with 25 μM of thymoquinone and 250 μM of ferulic acid, decrease proliferation of MDA-MB-231 cells	Al-Mutairi *et al*[38], 2021
	Ferulic acid	MDA-MB-231	Increased caspase 3 and reduced the proliferation of cancer cells about 40% at 100 μM. 100 mg/kg significantly reduced tumor volume, weight and growth in mice	Zhang *et al*[39], 2016
	Ferulic acid	4T1 cells	Reduced the growth of cancer cells at 500 μg/mL	Bagheri *et al*[40], 2017
	Galbanic acid	MDA-MB-231 and MCF-7 cells	IC50 was 48.7 and 56.6 μg/mL, respectively. Up-regulation of Bax and caspase-3 and down-regulation of bcl2	Sajjadi *et al*[42], 2019
	Galbanic acid	H460, A549, PC-9 and HCC827	IC50 calculated 100 μM on H460 cell line. Bax and caspase 9 increased and Bcl-2, Bcl-xL and myeloid cell leukemia 1 (Mcl-1) decreased in H460 cells	Oh *et al*[43], 2015
	Galbanic acid	AR+ PCa cells and AR- PCa cells	Suppresses the growth of AR (+) PCa cells. Inhibited cyclin/CDK4/6 pathway, specially cyclin D1	Zhang *et al*[44], 2012
	Farnesiferol C	HUVEC and mouse Lewis lung cancer cells	10-40 μmol/L inhibited VEGF. Reduced the growth of mouse Lewis lung cancer by 60%	Lee *et al*[45], 2010
	Sesquiterpene coumarins	PC-3 and MCF-7	Gummosin showed highest cytotoxic activity. Also showed an IC50 values at 30 and 32.1 μg/mL against PC-3 and MCF-7 cell lines respectively	Iranshahy *et al*[48], 2019
	Farnesiferol C	MCF-7	Decrease cell viability after 24, 48 and 72 h. (IC50 43, 20 and 14 μM, respectively), and stopped the cell cycle in G0/G1 phase and induced apoptosis in MCF-7 cells	Hasanzadeh *et al* [46], 2017

AGS: Aerobic granular sludge; BCL2: B-cell lymphoma 2; EMT: Epithelial-mesenchymal transition; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor.

ANTICANCER EFFECT OF NANOPARTICLES CONTAINING *FERULA ASSA-FOETIDA*

Encapsulation of essential oils, extracts and plant derivatives can overcome their therapeutic limitations and lead to better stability, increased bioavailability and better efficacy[24]. The use of nanoparticles in cancer treatment is a new method that can be used to target treatment. *Ferula assa-foetida* has various biological compounds that make it a suitable candidate for use in cancer treatment. Various studies have been conducted on the effect of different derivatives and extracts of this plant on different cell lines of cancer cells and generally positive results have been obtained. For example, use of silver nanoparticles and ethanol extract of asafoetida caused a decrease in the survival rate of L6 cancer cells, and the IC_{50} value was calculated as 1 μg/mL[25]. Some studies have shown that nanoemulsion containing *Ferula assa-foetida* essential oil can cause apoptosis by increasing BAX expression and decreasing BCL-2 in MCF7 cancer cells. The lethality of this nanoparticle has been calculated based on IC_{50} equal to 64 μg/mL for MCF7 and 201 μg/mL for A2058. Also, a significant decrease in the expression of vascular endothelial growth factor (VEGF) at 32 μg/mL and vascular endothelial growth factor receptor (VEGFR) at 128 μg/mL was observed in MCF-7 cells treated with nanoemulsion. This nanoparticle was able to significantly reduce tumor indices in the murine model of induced breast cancer at a concentration of 100 mg/kg[26]. Lipid nanoparticles containing *Ferula assa-foetida* seed oil on NT-2 human cancer stem cells had an IC_{50} equal to 115.4 μg/mL. The morphometric results of blood vessels treated with these nanoparticles showed that the number of blood vessels was significantly reduced in concentrations of 250, 500 and 1000 μg/mL in a dose-dependent manner. Also, these nanoparticles increased the expression of TNF-α, P21, and Cas3[27]. Synthesis of silver nanoparticles (AgNPs) with aqueous extract of asafoetida on MCF-7 cells caused cell death in a dose-dependent manner and its IC_{50} was calculated as 2 μg/mL[28]. By making zinc nanoparticles containing *Ferula assa-foetida* extract and investigating its effects on MCF7, MDA-MB231 and HT-29 cell lines, Boskabadi *et al*[29] showed that this nanoparticle can significantly reduce the growth of cancer cells. The calculated IC_{50} was equal to 23, 41.26 and 143 μg/mL after 72 h, respectively. In addition, the results showed that the nanoparticle has apoptotic properties and antioxidant activity with an IC_{50} equal to 500 mg/mL. Expression of Bax and Bcl2 significantly up and down regulated respectively. Mokhtareeizadeh *et al*[30] founded that nanoparticles containing *Ferula assa-foetida* essential oil can inhibit the growth of HepG2 and A2780 cells with IC_{50} of 57 and 106.7 μg/mL respectively. These nanoparticles caused a significant decrease in angiogenesis in fertilized eggs at a dose of 125 μg/mL. Also it induced apoptosis and death of cancer tissue cells by regulating Caspase3 and 9, TNF-α, P53 and P21 in nude mice with breast cancer.

ANTICANCER EFFECT OF ESSENTIAL OIL OF *FERULA ASSA-FOETIDA*

The main part used by *Ferula assa-foetida* is an oleo gum resin, which is obtained by shaving its root. This oleo gum resin contains many different compounds, the anti-cancer effects of some of these compounds have been investigated. The volatile part of oleo gum resin or its essential oil contains generally sulfur compounds that have a pungent and unpleasant smell. Some studies have shown that essential oil has strong anti-cancer effects. For example, Yatham *et al*[31] found four main compounds in asafoetida essential oil, including (-)-E-2-butylpropenyl disulfide, (-)-Z-2-butylpropenyl disulfide, (-)-1-(methylthio) propyl (E)-1 -Propenyl disulfide, and (-)-1-(methylthio) propyl (Z)-1-propenyl disulfide were identified and investigated their potential to inhibit the growth of cancer cell lines SKOV3 (ovary) and A549 (lung). Meanwhile, trisulfide showed better activity against A549 and SKOV3 cell lines compared to disulfides. The analysis of *Ferula assa-foetida* seed essential oil showed that it contains compounds such as E-1-propenyl sec-butyl disulfide (13.13%) Z-1-propenyl sec-butyl disulfide (11.34%). This essential oil exerted its inhibitory effect on aerobic granular sludge gastric cancer cells near 100% in 10μl/mL in 72 h after incubation[32]. The anti-proliferative and anti-apoptotic effects of asafoetida essential oil on liver cancer cell lines (HepG2 and SK-Hep1) as well as the expression of NFKB1, TGFB1, TNF, and caspase3 genes showed that the IC_{50} of the oil for HepG2 and SK-Hep1 was 7.21 μg/mL and 8.0 μg/mL respectively. After EO treatment, the genes involved in metastasis and proliferation decreased and the genes involved in apoptosis showed a significant increase (casp3 and TNF). Analysis of the essential oil by GC showed the presence of 1, 2-dithiolane in the amount of 87.4%[33]. Pavela *et al*[34] evaluated the essential oils asafoetida and *Ferula gummosa* on T98G (human glioblastoma multiforme cell line), HCT116 (human colon cancer cell line). *Ferula assa-foetida* essential oil was more active on HCT116 with IC_{50} value of 5.96 μg/mL and *Ferula gummosa* essential oil showed more activity on T98G with IC_{50} value of 4.49 μg/mL. Essential oil of asafoetida (EOA) exposed MCF7 cells to different concentrations of EOA (2, 4, 6, 8, and 10 μl/mL) at 24, 48 and 72 h showed that EOA significantly decreased the viability of MCF7 cells in a time and concentration-dependent manner. The

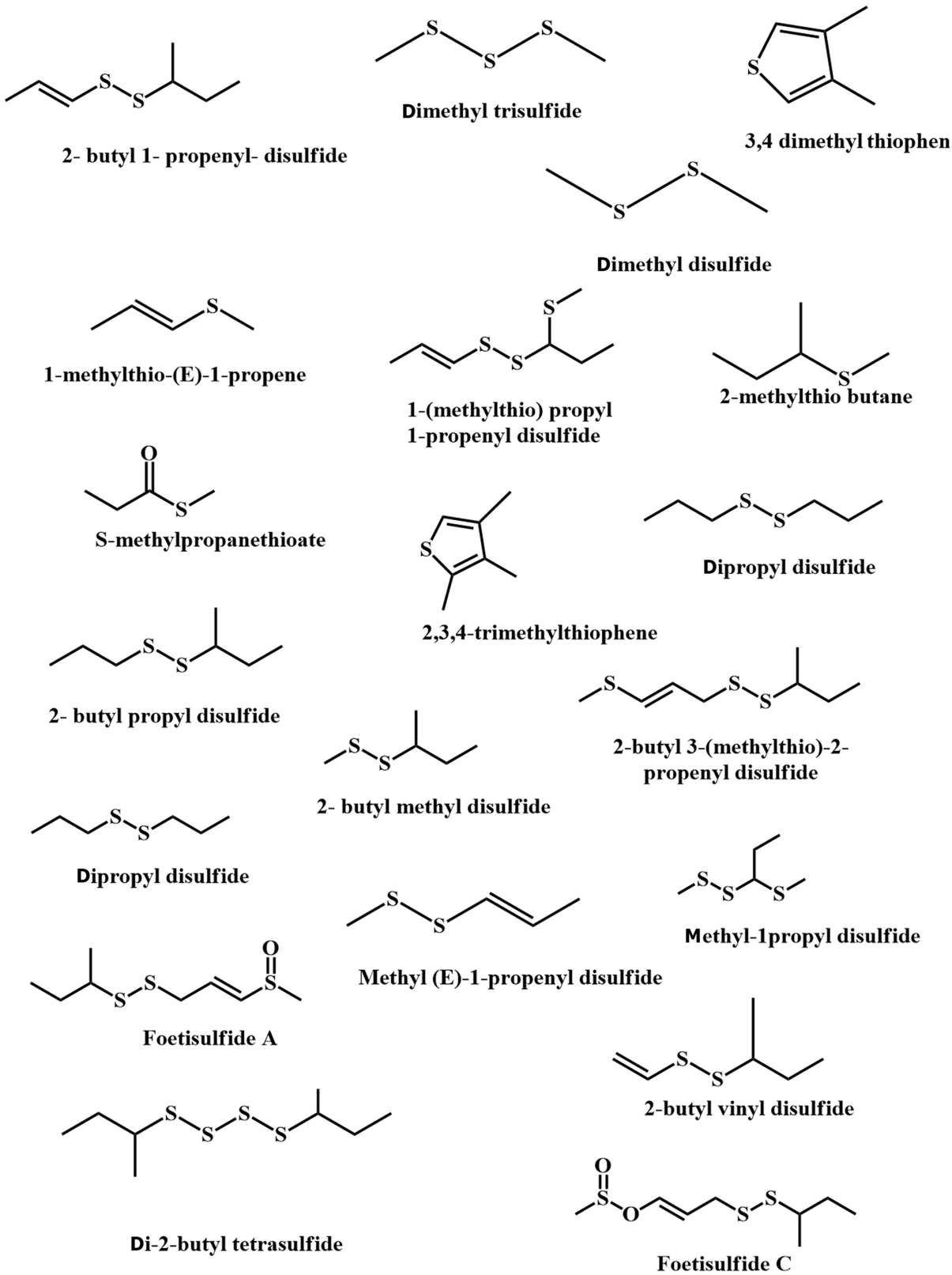

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Figure 1 Chemical structure of some sulfide compounds derived from Ferula assa-foetida.

major constituents identified in EOA were E1propenyl secbutyl disulfide (36.15) and Z1propeny secbutyl disulfide (27.93%)[35]

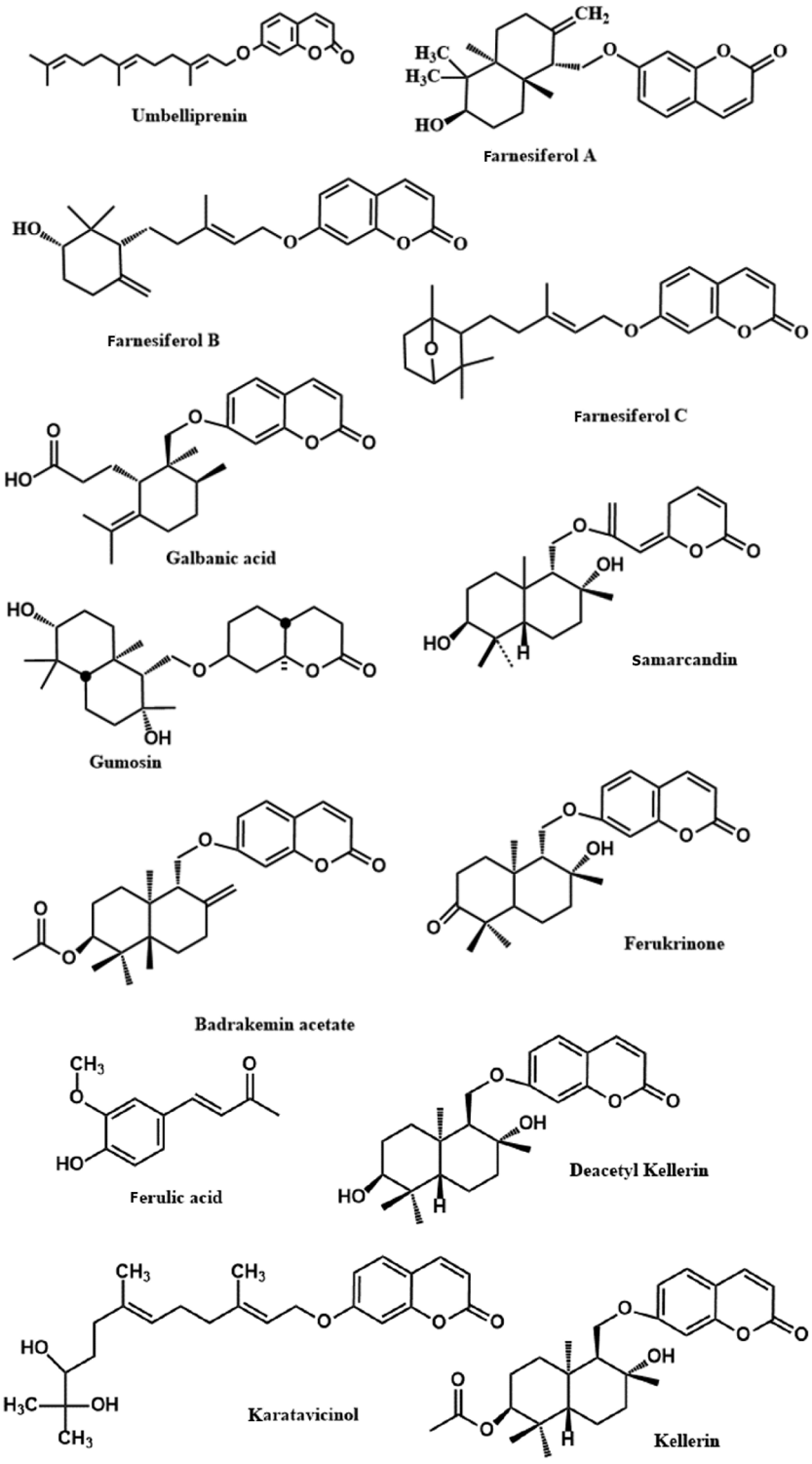

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Figure 2 Chemical structure of isolated constituents from *Ferula assa-foetida* showed anticancer effect.

ANTICANCER EFFECT OF ISOLATED CONSTITUENTS FROM *FERULA ASSA-FOETIDA*

Several compounds are derived from *Ferula assa-foetida*, which include coumarins, sesquiterpene coumarins, flavonoids and phenolic constituents that have shown a number of pharmacological effects, including antibacterial, antifungal, cytotoxic, antioxidant and hormonal activities, as well as anticancer effects[36]. Ferulic acid is one of the phenolic compounds in asafoetida, which has various therapeutic effects[37]. Al-Mutairi *et al*[38] have shown that when ineffective doses of ferulic acid were used with ineffective doses of thymoquinone, it was able to significantly reduce the death of MDA-MB- cells after 48 h. In another study, ferulic acid increased caspase 3 activity in the breast cancer cell line MDA-MB-231 and reduced the proliferation of the cancer cell line about 40% after 72 h at a concentration of 100

μM. Also, the anti-tumor potential of ferulic acid in a xenograft mouse model with MDA-MB-231 at a concentration of 100 mg/kg body weight could reduce tumor volume, weight and growth[39]. Bagheri *et al*[40], showed that ferulic acid significantly reduced the growth of 4T1 mouse breast cancer cells at a dose of 500 μg/mL. Galbanic acid is a terpenes lactone derived from the gum of *Ferula assa-foetida*, which has also been identified in several other species of Ferula[41]. Treatment of MDA-MB-231 and MCF-7 cells with galbanic acid showed that this compound leads to the inhibition of proliferation and induction of apoptosis with IC_{50} of 48.7 and 56.6 μg/mL, respectively. Also, galbanic acid stimulated apoptosis through the up-regulation of Bax and caspase-3 and the down-regulation of bcl2 and increased the expression of superoxide dismutase, catalase and glutathione peroxidase genes[42]. In confirmation of these results, in another study, the potential of galbanic acid in inhibiting four types of non- small lung cancer cells H460 and A549, PC-9 and HCC827 were proven after 24 h. Meanwhile, H460 cell line has the highest sensitivity to galbanic acid and showed an IC_{50} of about 100 μM. It was also found that the expression levels of Bax and caspase 9 increased and Bcl-2, Bcl-xL and myeloid cell leukemia 1 (Mcl-1) decreased and cleaved poly (ADP-ribose) polymerase (PARP) in H460 cells[43]. Androgen receptor (AR) signaling is crucial for the initiation and progression of prostate cancer (PCa). In a study, it was found that galbanic acid preferentially suppresses the growth of AR (+) PCa cells compared to AR (-) PCa cells. Galbanic acid induces apoptosis through G1 arrest associated with inhibition of cyclin/CDK4/6 pathway, especially cyclin D1[44]. The anti-angiogenic activities of farnesiferol C (FC) in human umbilical vein endothelial cells showed that exposure to a concentration range of 10-40 μmol/L FC inhibited VEGF, migration, invasion cells and decrease the expression of matrix metalloproteinase 2. Furthermore, FC inhibited the angiogenesis of mouse aorta treated with VEGF in an experimental model. FC reduced the growth of mouse Lewis lung cancer by 60% and caused rapid inhibition of VEGFR1 autophosphorylation caused by VEGF without affecting VEGFR2. However, FC inhibited the phosphorylation of most VEGFR2 downstream kinases such as focal adhesion kinase, Src, extracellular signal-regulated kinase 1/2, p38 mitogen-activated protein kinase, and c-jun-NH2-kinase without affecting AKT[45]. Sesquiterpene coumarins are a group of compounds found in the genus Ferula that have shown various therapeutic effects such as anticancer effects[21]. Farnesiferol C obtained from the chloroform extract of *Ferula assa-foetida*, on MCF-7 cells, led to a decrease in cell viability after 24, 48 and 72h. (IC50 43, 20 and 14 μM, respectively). Farnesiferol C stopped the cell cycle in G0/G1 phase and induced apoptosis in MCF-7 cells. This compound increased cellular SOD, CAT MDA activities in 24 and 48 h and reduced activity of SOD and CAT and increased MDA level after 72 h exposure. It demonstrated that reactive oxygen species level increased 5.92%, 13.53% and 14.43% after 24, 48 and 72 h exposure, respectively[46]. Treatment of K562, KBM5, U937 and HL-60 cancer cells with farnesiferol C showed that this substance has an IC_{50} = 10 μM on K562 cells and 20μM on KBM5 cells and showed a significant effect only on these two types of cells. Also, cleaved PARP and caspase 3 and 9 decreased the expression of Bcl2 and stopped cells in G1, and farnesiferol C decreased the expression of Cyclin D1, Cyclin E, Cyclin B1 and histone deacetylase 1 and 2 in K562 and KBM52 cells[47]. Investigation on anticancer potential of ten sesquiterpene coumarins include farnesiferol A, farnesiferol B, farnesiferol C, gummosin, samarkandin, umbelliprenin, badrakemine acetate, ferukrinone, kellerin and deacetyl kellerin derived from asafoetida showed that gummosin has highest cytotoxic activity among these sesquiterpene coumarins. It showed an IC_{50} values of 30 and 32.1 μg/mL against PC-3 and MCF-7 cell lines respectively[48]. Umbelliprenin is a prenylated coumarin compound found in Ferula species, also isolated from *Ferula assa-foetida*. This structure has various pharmacological effects such as cytotoxic activities and induction of apoptosis[49]. Using the umbelliprenin isolated from *Ferula assa-foetida* on Jurkat T-CLL and Raji B-CLL cell lines showed that umbelliprenin induced apoptosis in a dose- and time-dependent manner (IC50, 16 h = 75 μM and 48 h = 25 μM respectively)[50]. Farnesylation of the activated oncogenic ras product by Farnesyltransferase (FTase) is a critical step for its oncogenic function. Isolation of galbanic acid, karatavicinol, umbelliprenin, farnesiferol B, farnesiferol C from *Ferula assa-foetida* to inhibit FTase showed that galbanic acid has the highest enzyme inhibition potential and IC_{50} was calculated as 2.5 μM. In addition, the calculated IC_{50} value in reducing the proliferation of oncogenic ras-transformed NIH3T3/Hras-F cells by galbanic acid was 16.2 μM compared to the control group[51].

DIFFERENT EXTRACTIONS OF *FERULA ASSA-FOETIDA* ON CANCER

Ferula assa-foetida ethanolic extract showed a significant effect on PC12 and MCF7 cells in reducing cell survival. The amount of IC_{50}s for 24, 48 and 72 h for MCF7 was 1.30, 1.284, 0.753 μM, respectively. Also, IC_{50}s for PC12 category at 24, 48 and 72 h were calculated as 2.84, 0.8 and 0.4 μM, respectively[52]. The petroleum benzene, chloroform and methanol extract of asafoetida on MCF7 HepG2, A549, HT-29 and MDBK showed that the methanol fraction has an IC_{50} of more than 100 μg/mL. Petroleum and chloroform extracts showed IC_{50} values less than 52 μg/mL in four cell lines. Chloroform fraction showed IC_{50} equal to 61.42 μg/mL in MCF7. The petroleum afraction showed an IC_{50} of 45.73 μg/mL in MCF7[53]. The hydroalcoholic extract of *Ferula assa-foetida* significantly reduce the mRNA expression level of epithelial-mesenchymal transition markers (vimentin, Snail1, Zeb1) and the anti-apoptotic

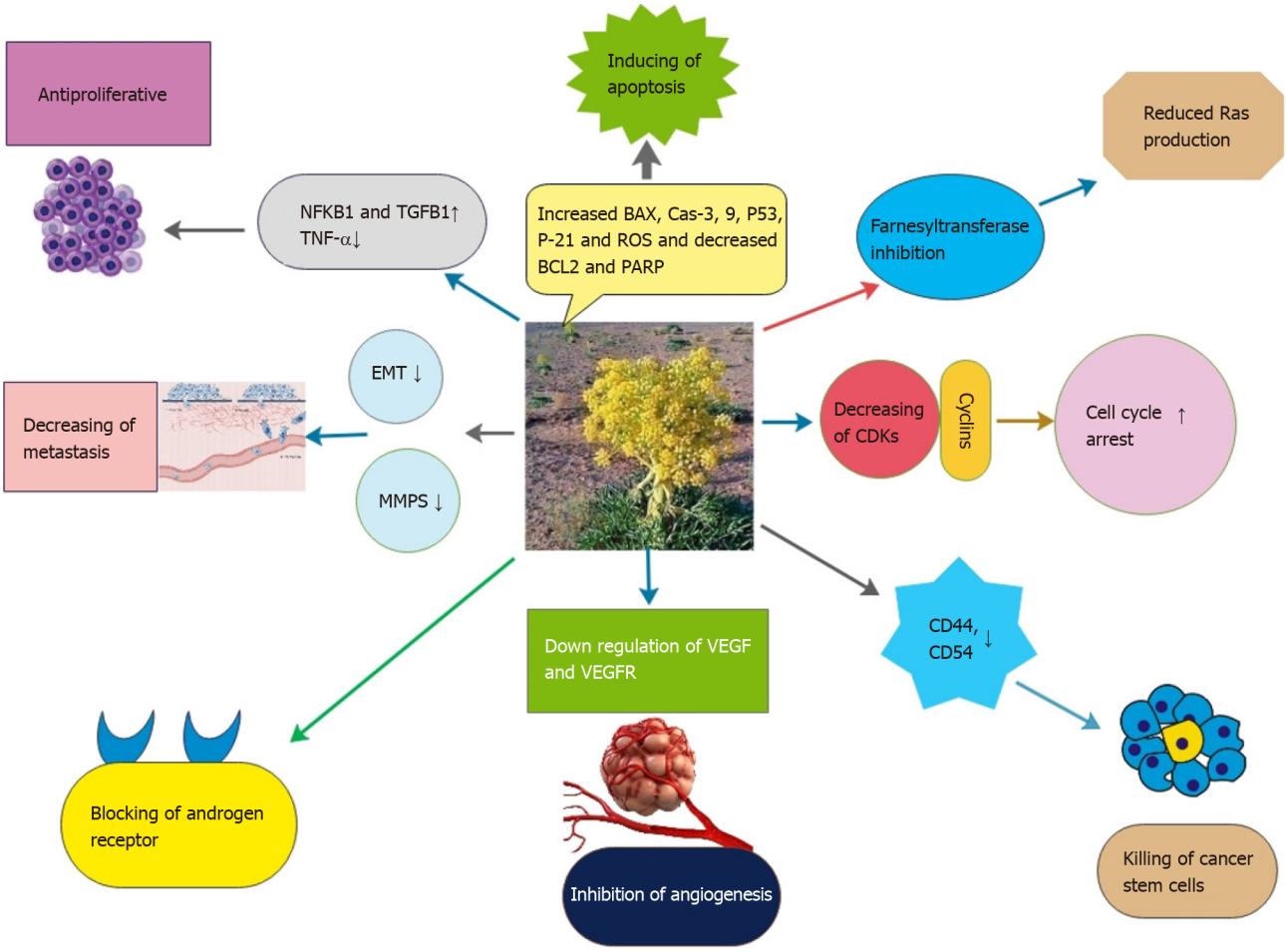

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Figure 3 Investigated mechanisms by which *Ferula assa-foetida* exerts its anticancer effects. BCL2: B-cell lymphoma 2; CDKs: Cyclin-dependent kinases; EMT: Epithelial-mesenchymal transition; MMPS: Matrix metalloproteinases; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor; ROS: Reactive oxygen species.

marker Bcl-2, as well as the expression of stem cell marker CD44 and CD54[54]. Ethanol extracts of *Ferula assa-foetida* and a number of its components (ferulic acid, vanillic acid, quercetin, ellagic acid, and p-coumaric acid) had cytotoxic effects on MCF-7 or MDA-MB-231 human breast cancer cells and 4T1 mouse cell line. Also, THP-1 peripheral blood monocytic leukemia cells can be polarized to M1 inflammatory phenotype by treatment with the extract and its components. Furthermore, this THP-1-dependent polarization of macrophages demonstrated an enhanced ability to damage MCF-7 or MDA-MB-231 cell monolayers in co-culture experiments. Therefore, treatment with *Ferula assa-foetida* extract can also indirectly cause the death of cancer cells through the activation of immune cells[55]. The cytotoxic effects of the ethanolic extract of Ferula assa-foetida resin on HepG2 cell line in concentrations (10, 50, 100, 200 μg/mL) showed that this extract in doses of 50, 100 and 200 μg/mL decreased the viability of HepG2 cells but in doses of 100 and 200, it also changes the shape of normal L929 cells. Therefore, only a dose of 50 μg/mL can be considered as an effective and non-toxic dose[56]. The investigation of methanolic and ethanolic extract of *Ferula assa-foetida* resin on osteosarcoma cell line showed that different concentrations of the extract in 24 and 48 h can reduce the survival of cancer cells. The highest effect rate corresponding to the concentration of 20 mg in 48 h for ethanolic and methanolic extract was calculated as 29.5 and 35.2, respectively. Also, the results showed that the ethanolic extract has a greater effect on the death of cancer cells[57].

ANIMAL EVIDENCES FROM ANTI-TUMOR EFFECT OF *FERULA ASSA FOETIDA*

Although animal evidence for the anticancer effect of *Ferula assa-foetida* is not much, several limited studies have shown that this plant has good anticancer potential. In a study, it was found that the use of 100 mg/kg asafoetida for 21 d against breast cancer caused by 4T1 cells in BALB/c mice can reduce tumor weight and tumor volume and increase the weight of treated mice. Also, asafoetida reduced lung, liver and kidney metastasis respectively. Asafoetida showed significant inhibitory activity against

lipoxygenase as well as antioxidant activity[15]. The use of food containing asafoetida (1.25 and 2.5%) showed that asafoetida significantly restored the level of the antioxidant system MNU (N-methyl-N-nitrosourea) induced mammary carcinogenesis in Sprague-Dawley rats. Furthermore, only in the MNU-control group, all animals had tumors with an average of 5.45 tumors per mouse (tumor burden) at the end of 18 wk, but the tumor burden in treated groups (1.25% and 2.5%) with asafoetida decreased to 3.6 and 2.3 tumor/mouse, respectively. The tumor volume in treated groups also decreased to 1.9cc (40%) and 1.3cc (59%), respectively, compared to 3.2cc in control group[58]. The use of different doses of asafoetida (5, 10 and 20 mg/100 g body weight) on dimethylhydrazine-induced colon cancer in rats showed that body weight, tumor frequency, tumor incidence, tumor size, total serum sialic acid as well as the tissue structure of the colon improved in all groups treated with asafoetida and these effects was better at dose of 10 mg/ 100 g body weight than other doses[59].

ANTICANCER MECHANISMS

The results of this study show that extracts and compounds isolated from Ferula asafoetida can cause the death of cancer cells in different ways. These mechanisms are briefly shown in Figure 3. As can be seen from this diagram, by reducing angiogenesis, increasing apoptosis, inhibiting metastasis, affecting the oxidative system of cancer cells and disrupting the cycle of cancer cells, *Ferula assa-foetida* causes damage and death of these cells.

CONCLUSION

Cancer is one of the serious problems of human society, especially in developing countries. The costs of treating the disease are very high and the death rate caused by it is worrying. The healthcare system and the research community should find effective and low-cost treatment methods as soon as possible, especially for poor communities. Finding anti-cancer compounds of natural origin is one of these solutions. It is very encouraging to see the results of the anti-cancer effects of *Ferula assa-foetida*. These results show that asafoetida can be considered as a medicinal plant in cancer treatment. Many of the effective compounds found in plant gum have anti-cancer effects, which can be inspired by these compounds to create new drugs. The use of asafoetida as a seasoning in foods can also be effective in the follow-up of cancer. By taking advantage of new methods such as nanotechnology and biotechnology, we can imagine a better perspective in using this plant and its derivatives as an anti-cancer agent.

FOOTNOTES

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