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Original Article

Anticancer Effect of Essential Oil of Seed of Ferula *Assa-foetida* on Adenocarcinoma Gastric Cell Line

Seyyed Majid Bagheri[1,2,*], Alia Shahmohamadi[3]

ABSTRACT

Background and Aim: Gastric cancer is a leading cause of cancer-associated mortality in men and the incidence is also on the rise in the entire world. The present study was aimed to investigate the chemical composition of essential oil of the seed of *Ferula assa-foetida* (EOSF) and anticancer activity of the oil on adenocarcinoma gastric (AGS) cell line. **Methods:** For evaluation of the cytotoxicity effect of EOSF, AGS cells were exposed to EOSF at different concentration and for different time durations. The 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay were carried out to characterize the cytotoxicity of the EOSF on AGS cells. In this study, the EOSF was obtained and analyzed by gas chromatography–mass spectrometry (GC-MS). **Results:** Our MTT assay showed that EOSF has a significant cytotoxicity activity in a time and concentration dependent manner. The main constituents of EOSF were alpha-D-Xylofuranoside, methyl 2, 5-di-O-methyl- (30.2%), E-1-propenyl sec-butyl disulfide (13.13%) Z-1-propenyl sec-butyl disulfide (11.34%). **Conclusion:** We conclude that the studied oil have a strong anticancer effect against AGS cell line. Based on the overall strong inhibition effects of the oil, isolation and studying of its compounds is suggested.

Key words: *Ferula assa-foetida*, Seed, Gastric cancer, Essential oil, Anticancer activity.

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INTRODUCTION

Cancer is one of the leading causes of death and more than seven million deaths occur in a year, worldwide.[1] In cancer cells, cell cycle control becomes deregulated and cells have an imbalanced proliferation to apoptosis ratio.[2] Gastric cancer originates from the glandular epithelium of gastric mucosa and according to global cancer statistics, gastric cancer is the fourth most frequently diagnosed cancer in men and the third most common cause of cancer-related death.[3] Currently, there are some inefficient treatments for cancer, including surgery, radiotherapy and chemotherapy; therefore, searching to find new effective therapies and anti-cancer drugs is one of the most important aims in medicine and pharmacology, respectively.[4] In recent years, due to relatively inexpensive and nontoxic properties of phytochemicals or chemopreventive agents with anti-cancer effects, the interest in herbal medicine has increased and more than 3000 plant species have been used to treat cancer.[5] Some chemopreventive agents in combination with chemotherapeutic agents can enhance their anti-cancer effects at the lower doses and reduce chemotherapy-induced toxicity.[6] *Ferula assa-foetida* L. is herbaceous plant of the umbelliferae family that grows wildly in the central area of Iran.[7] It is traditionally used in the treatment of hysteria, some nervous conditions, bronchitis, asthma and whooping cough.[8] The pharmacologically important part of this plant and several other species of *Ferula* is an oleo-gum-resin (asafoetida) obtained from incisions in the stem and/or roots of these plants.[9] In Iranian folk medicine, asafoetida is used as a diuretic, antispasmodic, carminative and analgesic agent.[10] Recent pharmacological and biological studies have also shown several pharmacological activities such as antioxidant,[11] antileishmanial,[12] cancer chemopreventive[13] anticonvulsant,[14] anti-inflammatory,[15] anti-diabetic,[16] antispasmodic,[9] hypotensive,[17] and antinociceptive[18] for asafoetida. Although there are a numerous studies about pharmacological effects of asafoetida, there are few studies about properties of the seed of *Ferula assa-foetida*. In a previous study, researchers reported the antifungal activity of oil seed against some pathogenic fungi.[19] Kassis *et al*. examined ethanolic extract of seed and root of *Ferula assa-foetida* that was called "Masculine" on male fertility and sexual functioning in rats and humans.[20] They showed that Masculine exhibits a high level of safety in rats, humans and cultured human fibroblasts and increases erection in rats. Bagheri *et al*. reported that essential oil of the seed of *Ferula assa-foetida* (EOSF) has antispasmodic effect and this effect was stronger than oleo-gum-resin of *Ferula assa-foetida*.[9] We also showed the essential oil of seed of *Ferula assa-foetida* exhibited a significant antinociceptive effect on chronic and acute pain in mice and concluded that

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these effects probably involve central opioid pathways and peripheral anti-inflammatory action.[21] In this work, we studied the GC-MS analyses and the anticancer activity of EOSF on adenocarcinoma gastric (AGS) cell line.

MATERIALS AND METHODS

Preparation of the Essential Oil from the Seed of *Ferula assa-foetida*

Two hundred grams of seeds of *Ferula assa-foetida* were gently grounded and mixed with 500 ml of double-distilled water. The essential oil was extracted by the hydro-distillation technique using a Clevenger apparatus. After extraction, the essential oil stored in hermetically sealed glass containers with rubber lids, covered with aluminum foil to protect the contents from light and kept under refrigeration at 4°C until used.[21]

Cells and Reagents

The AGS cells purchased from the Pasteur Institute of Iran, were maintained in Dulbecco's modified Eagle's medium (DMEM) (Gibco, USA) containing 10% (v/v) fetal bovine serum (FBS, Gibco Laboratories), 300 µg/ml glutamine, 100 µg/ml streptomycin and 100 units/ml penicillin. The cell cultures were maintained at 37°Ċ in a humidified atmosphere with 5% CO_2. The 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) were obtained from Sigma, USA.

Cytotoxicity Assay

Tumor cells were harvested from culture flasks using 0.05% Ethylenediaminetetraacetic acid (EDTA, Gibco Laboratories) for 3 min. The cells were washed in standard growth medium and counted using a hemocytometer. A number of 2×10^4 cells per well were plated on 96-well flat-bottomed plates. After one day of seeding of cells at 37°C, cells were treated for 24, 48 and 72 h with various concentrations of essential oil (0.01, 0.1, 1, 10 µl/ml). Cells treated with serum-free medium for the same period of time were used as a control. After that, the MTT solution (5 mg/ml in PBS) was added to each well. The MTTs was dissolved in sterile phosphate-buffered saline at 5 mg/ml and stored in dark environment at 4°C for a period lasting less than 3 weeks. After the final dilution, with pre-warmed sterile un-supplemented culture medium, the MTT solution was filtered through a 0.22µm filter. After 3.5 h of incubation, purple crystals were formed by mitochondrial dehydrogenase enzyme of living cells. Then, the medium was discarded and 150 µl of dimethyl sulfoxide (DMSO) was added to dissolve the formazan crystals. The absorbance of each sample was read at 540 nm using a micro plate reader (Bio Tek Instrument, Box 998). Results were expressed as percentage of cell viability with respect to untreated control cells (as 100%). The percent viability of each cell was calculated from the following formula:

$$\text{Percent viability}=\frac{\text{absorbance of test-absorbance of blank}}{\text{absorbance of control-absorbance of blank}}\times100$$

Lipoxygenase Inhibition Activity of EOSF

The soybean 15-lipoxygenase was used to test the 15-lox inhibitory activity of EOSF. For this purpose, 50 mL of essential oil solution was added to test solution containing 3 ml of phosphate buffer (0.1 M, pH = 8), 50 mL enzyme solution (final concentration of 167 U/ml) to achieve the enzyme inhibition between 20 to 80%. After 4 min incubation of test solution, the substrate (Linoleic acid, final concentration of 134 mM) was added and the change in absorbance was measured for 60 sec at 234 nm. The half maximal inhibitory concentration (IC_{50}) value was calculated graphically using the slopes of absorbance curves. The enzyme solution was kept in ice and tested at intervals to ensure that the enzyme activity was constant. All experiments were performed by UV/Vis Unico Double Beam Spectrophotometer at 25°C in triplicate.[13]

Antioxidant Activity Assay of Asafoetida

The antioxidant activity of EOSF was evaluated spectrophotometrically using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method. EOSF was evaluated at 100 mg/L, by mixing 0.75 mL with 1.5 mL of a freshly prepared DPPH solution (20 mg/L); then, sample was mixed thoroughly and kept in the dark for 30 min at room temperature. After that, each mixture was tested for the DPPH radical-scavenging activity by reading the absorbance at 517 nm on a spectrophotometer. Blank [solution prepared by mixing 0.75 mL of ultra-pure water with 1.5 mL of the DPPH solution (20 mg/L)] was used and read at the same wavelength. The antioxidant activity percentage was calculated following the formula:

Antioxidant activity (%) = [(A Control -A oil) /A Control] x 100

Where A Control is the absorbance of a DPPH solution without the oil, A oil is the absorbance of the tested oil, which is equal to the absorbance of the oil plus the DPPH (20 mg/L) minus the blank extract absorbance. The samples were run in triplicate and the average of the three values was recorded.[22]

Gas Chromatography-Mass Spectrometry Analysis

The chemical composition of the essential oil was determined at the Isfahan University of Medical Sciences by GC-MS using a Hewlett-Packard 5971 GC/MS apparatus (Avondale, PA, USA) under the following conditions: a 0.25 mm x 30 m polydimethylsiloxane DB-1 fused silica capillary column, with a film thickness of 0.10 µm; helium as the carrier gas helium (1 mL/min), injector temperature of 250°C and detector temperature of 200°C. The column temperature ranged from 35 to 180°C/min, at 4°C V/min and then from 180 to 280°C, at 20°C V/min; mass spectra were obtained by electronic impact 70 eV. The constituents were identified by a computer-based library search, with retention indices and visual interpretation of the mass spectra.[23]

Statistical Analysis of Data

Statistical data were assessed with one-way analysis of variance (ANOVA), followed by post hoc Tukey's test using Graph pad prism version 5. Results were expressed as mean ± standard error of the mean (SEM). A value of $P<0.05$ was considered significant.

RESULTS

Cytotoxic Effect of EOSF on AGS Cell Line

To determine whether EOSF has antiproliferative effect, AGS cells were treated with various concentrations (0.01, 0.1, 1, 10 µl/ml) of the EOSF for the indicated times (24, 48 and 72) and cell proliferation was determined using the MTT-based colorimetric assay. As duration and dose increases, proliferation was significantly decreased in cells treated with the EOSF, clearly demonstrating an antiproliferative effect (Figure 1). The inhibition effect of EOSF on AGS cells was enhanced after incubated for 24, 48 and 72h.

Chemical Constituents

Analysis of the chemical composition of the essential oil by GC-MS facilitated the identification of oil components. The major compounds identified in EOSF were alpha-D-Xylofuranoside, methyl 2,5-di-O-methyl-(30.2%), E-1-propenyl sec-butyl disulfide (13.13%) and Z-1-propenyl sec-butyl disulfide (11.34%) (Table 1).

Lipoxygenase Inhibitory and Radical Scavenging Activity

The lipoxygenase (LOX) activity was measured as an increase in the absorbance at 234 nm, which reflects the formation of hydroperoxylinoleic acid. The IC_{50} of inhibitory activity of EOSF was 38µg/ml and IC_{50} of antioxidant activity of EOSF was 112µg/ml (Table 2).

DISCUSSION

This study set out to investigate the anti-proliferative effects of EOSF against human AGS cell line. Our results revealed that 24, 48 and 72h after incubation with EOSF, cell viability was significantly decreased as dose of EOSF and time of incubation increases compared to control group (Figure 1). The cytotoxic activity of the EOSF on AGS cell line using MTT assay suggested that the oil is severely cytotoxic on AGS cells. Due to this cytotoxic effect, mortality of the cells was near 100% in 10µl/ml in 72h after incubation. The anti-cancer potent and chemopreventive effects of *Ferula* species and its derivatives have investigated in different studies. Bamehr *et al.* indicated that *Ferula pseudalliacea* extract is able to induce apoptosis in HCT-116 cells mainly by induced apoptosis via promotion of cell cycle arrest, caspase 3 activation and destruction of mitochondria membrane potential.[24] A coumarin (diversin) isolated from the roots of *Ferula diversivittata* were studied for their possible anticancer effects and results of the investigation indicated that diversin might be valuable as a potent cancer chemopreventive agent.[25] Umbelliprenin is an another component that has shown a remarkable cancer chemoprevention *in vitro* and *in vivo* studies.[26] Researchers assessed the cancer chemopreventive activity of umbelliprenin *in vivo* by using a two-stage carcinogenesis assay of mouse skin tumors[26] and they found that cancer chemoprevention of umbelliprenin is comparable with curcumin, a well-known cancer chemopreventive agent. *Ferula assa-foetida* is one of the important *Ferula* species that grows wildly in central area of Iran and showed several biological and pharmacological activity.[27] The oleo gum resin is most important part of *Ferula assa-foetida* that often obtained by incision of the roots or removal of the stems and chemical compounds can be used for treating diseases including cancer.[28] The modulatory influences of *Ferula assa-foetida* oleo gum resin on the mammary epithelial tissue differentiation, hepatic drug metabolizing enzymes, antioxidant profiles and N-methyl-N-nitrosourea (MNU)-induced mammary carcinogenesis in Sprague-Dawley rats was investigated[29] and the findings indicated the chemopreventive potential of asafoetida against MNU-induced mammary carcinogenesis. Saleem *et al.* showed that pretreatment of animals with acetone extract of asafoetida could cause the reversal of early events of carcinogenesis *in vivo*.[30] Another study showed that asafoetida reduced the multiplicity and size of palpable mammary tumors in Sprague–Dawley rats.[8] Different mechanisms seem to impact on this activity such as radical scavenging activity and lipoxygenase inhibition activity[29] and blocking the enzyme 5-lipoxygenase may be for at least part of the observed chemopreventive activity of the asafoetida and its components. Our results showed that EOSF also has remarkable antioxidant and lipoxygenase inhibitor activity. Analysis of the chemical composition of the SEOF by GC-MS showed that the oil consists of mainly alpha-D-Xylofuranoside, methyl 2,5-di-O-methyl, E-1-propenyl sec-butyl and Z-1-propenyl sec-butyl. Previously, some evidence suggests that organosulfur compounds modulate the activity of several metabolizing enzymes that activate (cytochrome P450s) or detoxify (glutathione S-transferases) carcinogens and inhibit the formation of DNA adducts in several target tissues.[31] Sulfur compounds contained within vegetables may be chemically or enzymatically transformed in the human body with subsequent formation of hydrogen sulphide (H_2S) and their consumption has been associated to chemopreventive effects.[32] Furthermore, epidemiological studies have shown that people assuming

Table 1: Chemical Composition of Essential Oil of the Seed of *Ferula assa-foetida*.

	Library/ID	Pct Total
1	.alpha.-D-Xylofuranoside, methyl 2,5-di-O-methyl-	30.2
2	(E)-sec-Butyl propenyl disulfide	13.13
3	(Z)-sec-Butyl propenyl disulfide	11.34
4	Trifluoromethyl t-butyl disulfide	6.33
5	Disulfide, bis(1-methylpropyl)	5.47
6	10-epi-.gamma.-eudesmol	4.37
7	3-Mercaptopropionitrile	3. 28
8	Agarospirol	3.5
9	Ethanethioamide	2.9
10	Methyl sec-butyl disulphide	2.75
11	5-epi-7-epi-α-Eudesmol	2.62
12	1-(Methylthio) propyl propyl disulfide	2.53
13	(-)-Aristolene	1.41
14	(Z)-1-(But-2-en-1-yl)-2-(sec-butyl)disulfane	1.3
15	.alpha.-Pinene	1.8
16	3H-1,2-Dithiole	1.9
17	N-propyl sec-butyl disulfide	0.44
18	4-(hexadecyloxy)-3-nitrobenzenesulfonyl fluoride	0.39
19	Thiopivalic acid	0.36
20	Benzenepropanoic acid, pentyl ester	0.33
21	2-Thiazolidinethione	0.27
22	Morpholine, 2,6-dimethyl-	0.25
24	Tridecyloxirane	0.19
25	Elemol	0.17
26	Dimethyl trisulfide	0.17
	Total	94.22

Table 2: Antioxidant and Lipoxygenase Inhibitory Activities of EOSF.

DPPH (IC_{50})	Lipoxygenase Inhibition (IC_{50})
112 µg/ml	38 µg/mL

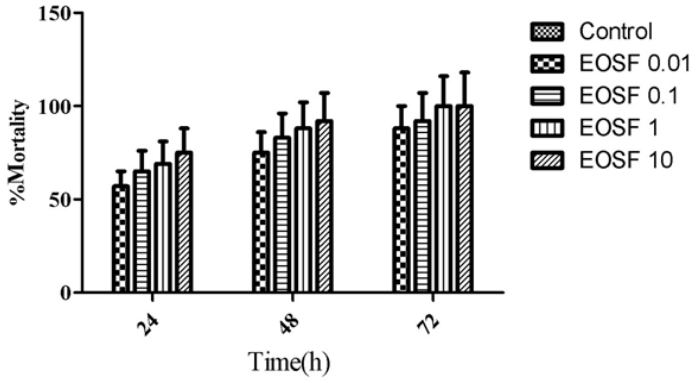

Figure 1: Cytotoxicity Effect of EOSF on AGS Cells after 24, 48 or 72h Incubation.
Data was expressed as Mean ± S.E.M
EOSF: Essential oil of seed of *Ferula assa-foetida*

a diet rich in cruciferous vegetables have a minor incidence of breast, lung, prostate, colon and bladder cancer.[33] Phytochemicals rich in sulfur, in particular diet-derived compounds, have therefore been proposed and applied in clinical trials as cancer chemo preventive/ chemotherapeutic agents. These results along with studies performed using inhibitors of the enzymes responsible of H_2S production have led to hypothesize a role for this metabolic pathway in cancer.[34]

CONCLUSION

EOSF has inhibitory effect on the growth of AGS cell line and could be considered as attractive alternative to serve as compounds in drug development for gastric cancer as an adjuvant therapy. Hence, the oil can be utilized safely for therapeutic use in pharmaceutical formulations.

CONFLICT OF INTEREST

Authors declare that they have no conflict of interest

ABBREVIATIONS

EOSF: Essential Oil of the Seed of *Ferula assa-foetida;* **AGS cell line:** Adenocarcinoma Gastric cell line; **MTT:** 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide; **GC-MS:** Gas Chromatography–Mass Spectrometry; **DMEM:** Dulbecco's Modified Eagle's Medium; **FBS:** Fetal Bovine Serum; **EDTA:** Ethylenediaminetetraacetic acid; **IC_{50}:** Half Maximal Inhibitory Concentration; **DDPH:** 2,2-diphenyl-1-picrylhydrazyl; **LOX:** Lipoxygenase; **MNU:** N-methyl-N-nitrosourea; **H_2S:** Hydrogen Sulphide.

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