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EVALUATION OF THE CYTOTOXICITY EFFECTS OF ETHANOLIC EXTRACT OF FERULA ASSAFOETIDA RESIN ON ORAL SQUAMOUS CELLS CARCINOMA (KB) COMPARED WITH L929 CELLS

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Abstract

One of the most common forms of malignancy is oral squamous cell carcinoma (OSCC). Despite advances in cancer treatment, the mortality rate of OSCC has remained almost unchanged for the past decades. Improving treatment requires the search for new classes of safer and more effective anticancer agents. Oleo-gum-resin obtained from Ferula assafoetida has significant anticancer properties against various cancer cells. The current study aims to evaluate the cytotoxic effects of the oleo-gum-resin extract on oral squamous cell carcinoma (KB) compared with normal mouse fibroblast cells (L929). The KB (cancer group) and L929 (control group) cells were cultured in an enriched RPMI-1640 medium. Then the cells were treated with 5 - 160 µg/ml concentrations of oleo-gum-resin extract for 24, 48, and 72 hours. The cell viability rate was determined by MTT assay. The statistical data analysis was done using SPSS software and the one-way ANOVA technique. Tukey's comparison procedure was used to compare individual means. A t-test was used to compare the identical concentrations between two cell lines. In this study, IC_{50} was 37.36 and 89.81 µg/ml for KB and L929 cells, respectively. The IC_{50} ratio for normal (L929)-to-tumoral (KB) cells was 89.81: 37.36 = 2.40, indicating that a 2.5-fold higher effect of asafoetida extract on normal mouse fibroblast cells (L929) compared tumoral cells (KB). According to the results, the ethanolic asafoetida extract exhibited more cytotoxic effects on KB than on L929 cells. This study demonstrated that the asafoetida extract exerted more cytotoxic effects on oral squamous cell carcinoma than normal cells.

Keywords: *Anticancer, Cancer, cytotoxicity, Herbal medicine, In vitro, Oleo-gum-resin*

Introduction

Cellular abnormality, also known as cancer, is characterized by uncontrolled cell growth and division [*Otto T, Sicinski P, 2017*] with many possible causes. The World Health Organization (WHO) noted that cancer is the second leading cause of death in many nations [*Bray F et al., 2018; Hunter DJ, Reddy KS, 2013*] and that by 2040, there may be 27.5 million new cases of cancer annually

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[*Dosanjh M et al., 2022*]. Oral squamous cell carcinoma (OSCC) is one of the most prevalent types of cancer and can develop anywhere in the mouth and oropharynx [*Graham S et al., 1977*]. OSCC is associated with a variety of etiological and predisposing risk factors, including long-term tobacco use, alcohol consumption, ultraviolet (UV) radiation (especially in lip cancer), genetic predisposition, candidiasis, human papillomavirus (HPV), and hepatitis C virus (HCV) infections, as well as poor dietary control and nutritional deficiencies (especially vitamin and mineral deficiency) [*Johnson NW et al., 2011; Marur S et al., 2010; Nagao Y, Sata M, 2009; Poeta ML et al., 2007*]. The mortality rates of OSCC have remained relatively unchanged for recent decades, despite improvements in surgical techniques and other cancer treatments like chemotherapy and radiotherapy, which are highly efficient and widespread techniques in cancer treatment [*Marur S et al., 2010*]. Additionally, these cancer treatments are associated with short- and long-term side effects [*Qi F et al., 2010*] , and there has been growing concern about the unintended consequences and side effects [*Islam KM et al., 2019*]. Hence, it is necessary to find new types of safe and more potent anticancer drugs that operate via several pathways [*Kooti W et al., 2017*]. Admittedly, natural components have shown more reliable and secure outcomes [*Abdulridha MK et al., 2020; Greenwell M, Rahman PK, 2015*], and many research studies have shown the pharmaceutical characteristics of herbal medicines to discover and develop new anticancer drugs [*Huang MY et al., 2018*]. *Ferula assafoetida* is a medicinal herb from the *Apiaceae* family. This plant's rhizome, rootstock, or taproot exudes oleo-gum-resin (latex), also known as asafetida [*Bafghi AF et al., 2014*]. Oleo-gum-resin has been traditionally used, as an anti-diabetic [*Abu-Zaiton AS, 2010*], antioxidant [*Dehpour AA et al., 2009*], antispasmodic [*Fatehi M et al., 2004*], anti-carcinogen [*Saleem M et al., 2001*], and also as a cancer chemopreventive [*Iranshahi M et al., 2008; Iranshahy M, Iranshahi M, 2011*]. The result of a meta-analysis study demonstrated that the rate of cancer in the countries with asafoetida usage is lower than the other countries (China, Russia, Japan, and Indonesia), where they don't use this oleo-gum-resin [*Nigam U, Sachan S, 2013*]. It has been shown that asafoetida has potential antimutagenic and antioxidant activity [*Iranshahy M, Iranshahi M, 2011*]. Also, some in vitro research studies revealed that F. assafoetida has cytotoxic activity against human cervical carcinoma, human hepatocellular carcinoma, and human colorectal adenocarcinoma [*Bagheri SM et al., 2010; Hamzeloomoghadam M et al., 2013*]. However, there is no research on the cytotoxicity effects of asafoetida on oral squamous cell carcinoma (KB). The purpose of this study was to assess the possible cytotoxic effects of asafoetida against oral squamous cell carcinoma under in vitro conditions.

Methods

Plant materials:

The oleo-gum resin (asafoetida) was collected from Kerman province, Iran, to prepare the ethanolic extract of asafetida. The 150 g of oleo-resin-gum dried thoroughly and ground into a powder. Then, 100 g of asafoetida powder was soaked in 1 liter of 70% ethanol at room temperature for 48 h. The incubated solvent was filtered (Whatman Grade 40) under the laminar flow hood to have a homogeneous solvent. A rotary evaporator was used to evaporate the solvent, and the extract was then collected and kept at 4 °C until needed.

In vitro *analyses*

Cells: The squamous cell carcinoma cells (KB) and normal mouse fibroblast cells (L929) were prepared at the Traditional Medicine Institute of Isfahan, Isfahan, Iran, and cultured in RPMI-1640 medium (SIGMA, USA) supplemented with 10% fetal bovine serum (FBS), 100 Unit/ml penicillin (Gibco) and 100 µg/ml streptomycin (Gibco, USA) and incubated in 5% CO_2 incubator at 37 °C.

Cytotoxicity assay determination using MTT assay: To determine the cytotoxicity effect of oleo-gum-resin (asafoetida) on squamous cell carcinoma cells (KB) and normal mouse fibroblast cells (L929), the 3-(4, 5 dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) salt (Roche Diagnostics GmbH, Germany) was used. This assay is according to mitochondrial enzyme succinate dehydrogenase (SDH) activity, which converts the yellow dye of MTT salt to insoluble violet formazan dye crystals [*Gavanji S et al., 2023; Vajrabhaya LO, Korsuwannawong S, 2018*], that

will be soluble by dimethyl sulfoxide (DMSO) [*Buttke TM et al., 1993*]. The 180 µl cell suspension at 5×10^4 cells/ml concentration was poured into 96-well flat-bottomed plates and incubated at 37 °C with 5% CO_2 for 24, 48, and 72 h. Each well contained a varied concentration of asafoetida ethanolic extract (5 to 160 g/ml). DMSO (Merck, Germany) at a concentration of 2% (v/v) was used as a negative control. Following that, 20 µL of MTT solution was added to each well at various incubation times, and cells were incubated in a humidified atmosphere with 5% CO_2 for 4 hours. Then, 100 DMSO was added to each well as a solubilization solution to dissolve the formazan crystals. The absorbance was measured at 560 nm. Half of the maximum inhibitory concentration (MIC) of asafoetida was determined to be the concentration at which the viability of the cells is reduced to half (IC_{50} value).

$$\text{Cell survival percentage} = \frac{\text{Test compound OD-Blank OD}}{\text{Negative control OD-Blank OD}} \text{x}100$$

STATISTICAL ANALYSIS

Data were statistically analyzed using SPSS software, version 20 (SPSS Inc., Chicago, IL, USA). One-way ANOVA was used to determine the statistical significance of differences between different extract concentrations, and Tukey's comparison procedure was used to compare individual means. The same concentrations between two cell lines were also compared using the t-test. The data were expressed as the mean ± standard error.

RESULTS

The cytotoxic effect of asafoetida extract at various concentrations and times (24, 48, and 72 h) has been examined in the current study. Asafoetida extract concentration could significantly decrease cell viability ($p<0.0001$). After 24 hours of exposure, the cytotoxic effect of asafoetida extract on KB cell lines became apparent starting at 10 g/ml (Fig. 1 *round markers*). Furthermore, the KB cell viability was significantly reduced after 24 and 48 hours of incubation at an 80 g/ml concentration, and the percentage of dead cells reached 100% (Fig. 1 *square markers*). Also, the cytotoxic effect of asafoetida extract on L929 cells emerged at 40 µg/ml after 24 h. This result showed that 140 µg/ml of extract had significant inhibitory effects. In this concentration, L929 cell viability reduced to

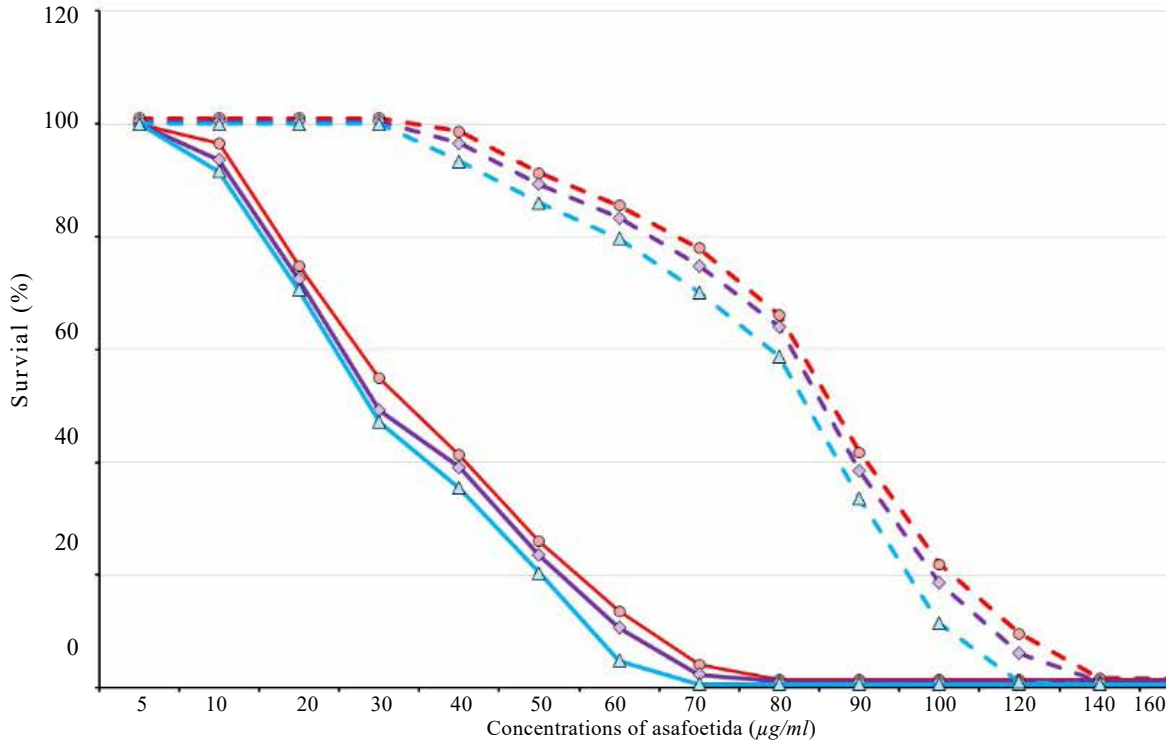

FIGURE 1. *Cytotoxic effect of different concentrations of asafoetida against KB (solid lines) and L929 (dashed lines) cells, after 24 h (round markers), 48 h (square markers) 72 h (triangular markers.*

Table 1.

Cytotoxic activity of different concentrations of asafoetida against the squamous cell carcinoma cells (KB) and normal mouse fibroblast cells (L929)

Concentrations of asafoetida (*µg/ml*)	Time (h)					
	24	48	72	24	48	72
	KB cell (Mean±SE)			L929 cell (Mean±SE)		
5	100±0.00^{a}	100±0.00^{a}	100±0.00^{a}	100±0.00^{a}	100±0.00^{a}	100±0.00^{a}
10	96.63±1.58^{a}	93.63±1.33^{a}	91.60±1.45^{b}	100±0.00^{a}	100±0.00^{a}	100±0.00^{a}
20	74.87±1.50^{b}	72.5±1.15^{b}	70.60±1.07^{c}	100±0.00^{a}	100±0.00^{a}	100±0.00^{a}
30	54.87±3.43^{c}	49.20±0.47^{c}	47.13±0.89^{d}	100±0.00^{a}	100±0.00^{a}	100±0.00^{a}
40	41.37±0.45^{d}	39.13±0.64^{d}	35.47±0.78^{e}	98.67±0.73^{ab}	96.63±0.67^{ab}	93.40±1.65^{b}
50	26.07±1.75^{e}	23.5±1.70^{e}	20.43±2.06^{f}	91.33±0.75^{bc}	89.27±0.65^{bc}	86.03±0.25^{c}
60	13.60±1.79^{f}	10.70±2.23^{f}	4.83±2.52^{g}	85.57±1.19^{c}	83.33±1.01^{c}	79.67±1.53d
70	4.00±1.43^{g}	2.33±1.03^{g}	0.00±0.00^{g}	78.00±0.81^{d}	74.87±0.64^{d}	70.17±0.71^{e}
80	0.00±0.00^{g}	0.00±0.00^{g}	0.00±0.00^{g}	66.13±2.92^{e}	64.03±3.29^{e}	58.80±0.52^{f}
90	0.00±0.00^{g}	0.00±0.00^{g}	0.00±0.00^{g}	41.73±1.47^{f}	38.47±1.05^{f}	33.53±3.15^{g}
100	0.00±0.00^{g}	0.00±0.00^{g}	0.00±0.00^{g}	21.90±1.83^{g}	18.63±1.83^{g}	11.43±1.72^{h}
120	0.00±0.00^{g}	0.00±0.00^{g}	0.00±0.00^{g}	9.60±1.76^{h}	6.13±3.10^{h}	1.00±1.00^{i}
140	0.00±0.00^{g}	0.00±0.00^{g}	0.00±0.00^{g}	1.67±0.71^{i}	0.00±0.00^{h}	0.00±0.00^{i}
160	0.00±0.00^{g}	0.00±0.00^{g}	0.00±0.00^{g}	0.00±0.00^{i}	0.00±0.00^{h}	0.00±0.00^{i}

Notes: $^{a, b, c, d, e, f, g, h, i}$ Different letters on every column represent the significant difference ($p < 0.0001$). SE, standard error

less than 99% after 24, 48, and 72 h (Fig. 1 *triangular markers*). The ethanolic extract of asafoetida had a higher cytotoxic effect against the cancer cell line than the normal cell line (Table 1).

IC_{50} values of asafoetida extract against KB and L929 cell lines were calculated at 37.36 and 89.81 µg/ml after 24 h, respectively (Table 2). For the KB and L929 cells, the calculated R^2 was 0.98 and 0.93, respectively. The results showed that the asafetida ethanolic extract inhibited the cancer cell line more potently than the normal cell line. It is possible to reduce the cell viability percentage in a dose-dependent manner. IC_{50} ratio for normal (L929)-to-tumoral (KB) cells was 89.81: 37.36 = 2.40, exhibiting a 2.5-fold cytotoxic effect of asafoetida extract on tumoral cells (KB) compared to normal mouse fibroblast cells (L929).

Table 2.

Assessment of IC_{50} and R^2 in KB and L929 cell lines

IC_{50} equation	
for KB cells	**for L929 cells**
y = -1.4125x + 102.78	y = -0.9311x + 133.62
R^2 = 0.98	R^2 = 0.93
IC_{50} = 37.36 µg/ml	IC_{50}= 89.81 µg/ml

Notes: R^2 ranges from 0 to 1, that the closer R^2 value to 1 demonstrates the better and the higher ability of this model. (X) is the asafoetida concentration.

Discussion

Currently, cancer multidrug resistance (MDR) is a considerable problem [*Bukowski K et al., 2020*]. Also, various side effects range is observed in cancer therapies [*Altun I, Sonkaya A, 2018*]. As a result, research into the assessment of novel compounds with anticancer potential is expanding. Natural compounds have been traditionally used in several diseases therapy [*Gavanji S, Larki B,*

2017]. Studies have revealed that asafoetida or oleo-gum-resin extracted from F. asafetida has cytotoxic properties and has been used in traditional medicine, such as cancer cell lines [*Bagheri SM et al., 2017a*]. The present study aimed to evaluate the possible cytotoxic effects of asafoetida against oral squamous cell carcinoma (KB) compared to normal mouse fibroblast cells (L929) under in vitro conditions. The current study showed that the toxicity and inhibitory effect of the ethanolic extract of the asafoetida on KB is significantly higher than on L929. At concentrations of 100% lethality for K29 cells, approximately 70-75% of L929 cells survive and the use of the extract for more than 24 hours at a concentration of 70-80 µg/ml can be practiced. It has been stated that asafoetida at 5 mg/ml concentration reduced osteosarcoma cell line (Hos crl) viability by less than 50 % [*Mohd Shafri MA et al., 2015*]. Bagheri SM et al. (2017) evaluated the effect of asafoetida essential oil on a breast cancer cell line (4T1). They found the essential oil at 0.01 µg/ml concentration significantly decreased the cell viability after 48 and 72 h [*Bagheri SM et al., 2017b*]. It can be stated that the asafoetida essential oil possessed a higher cytotoxic effect on the cancer cell line compared to the asafoetida extract. Asafoetida contains many phytochemicals, such as Farnesiferol and Umbelliprenin [*Iranshahy M, Iranshahi M, 2011*], which can be used as a cancer chemoprevention compound [*Iranshahi M et al., 2009*]. Also, another study indicated that Farnesiferol C possessed the therapeutic potential for cancer [*Choi YE, Park E, 2015*]. A research study showed that phenolic compounds of asafoetida had significate antitumor and antioxidant properties [*Yan X et al., 2002*]. Moreover, Iranshahy M et al. (2019) declared asafoetida has another chemical compound, including sesquiterpene coumarins. They measured the effect of asafoetida on the human breast adenocarcinoma cell line (MCF-7), human prostate cancer cell line (PC3), and human normal fibroblast cell line (NIH) [*Iranshahy M et al., 2019*]. A study by Sadooghi SD (2013) reported that asafoetida had a cytotoxic effect on the human liver cancer cell line (HepG2) and reduced the cell viability at 50 µg/ml concentration [*Sadooghi SD et al., 2013*]. The comparison between their result and ours revealed that asafoetida had a higher cytotoxic activity on oral squamous cell carcinoma (KB) than the human liver cancer cell line (HepG2). There were no significant differences among the cytotoxic concentration in L929 cells. Unnikrishnan and Kuttan showed that the asafoetida extract inhibited two-stage of chemical carcinogenesis and may be used as an antitumor medicine [*Unnikrishnan MC, Kuttan R, 1990*]. Panwar R et al. (2015) examined the chemopreventive effect of the asafoetida extract on 1,2-dimethylhydrazine, a carcinogen that induces colon carcinogenesis, in rats [*Panwar R et al., 2015*]. Their result demonstrated that oleo-gum-resin extract could attenuate the 1,2-dimethylhydrazine activity and inhibit colon cancer development as a chemopreventive material. Further study on the survival of KB and L929 cells, particularly at high asafoetida concentrations in less than 24 hours, is recommended.

Conclusion

The finding of this study showed that asafoetida extract had cytotoxic activity against KB. However, it demonstrated little cytotoxicity on normal cells. Therefore, further research on side effects and mechanism of action is required to provide vital insights regarding the oleo-gum-resin as a potential anticancer therapy.

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