Original Article

The Cytotoxic Effect of the Tarragon (*Artemisia dracunculus* L.) Hydroalcoholic Extract on the HT-29, MKN45, and MCF-7 Cell Lines

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ABSTRACT

Background:: Cancer is one of the problems facing societies today and despite new advances in chemotherapy and cancer treatment, there are still many cancers that do not respond to today's treatments. Tarragon with the scientific name of Artemisia dracunculus L. has various flavonoid and polyphenolic compounds and many therapeutic effects.

Objectives: This study aimed to investigate the cytotoxicity of this plant on different categories of cancer cels.

Methodes: After collecting the shoots of tarragon and extracting them by the maceration method, the weight of the extract with a yield of 22.25% was 12.9 g. After examining the presence of flavonoids and total phenol, the extract's antioxidant activity was examined using DPPH and FRAP methods. Finally, MTT tests on three cancer cell lines, MCF-7, HT-29, and MKN45, were done using different concentrations of tarragon extract (100, 200, 500, and 1000 µg/mL).

Results: Total flavonoids were detected at 24±1.18 mg of quercetin per gram of extract, and total phenols were detected at 59±2.21 mg of gallic acid per gram of extract. Examining the inhibitory effect of DPPH compared to vitamin C, it was found that the hydroalcoholic extract of tarragon has a 50% inhibitory effect. According to the standard curve, the amount of iron reduced by tarragon hydroalcoholic extract is equal to 405±0.11 µg/ml. The cytotoxic effect of tarragon hydroalcoholic extract on MCF7, MKN45, and HT-29 cell lines was investigated, and their IC50 values were 1065.669, 881.19, and 743.870 µg/mL, respectively. The A. dracunculus L extract inhibits the growth of cancer cells in various cell lines.

Conclusion: According to antioxidant tests, it can be said that the anti-cancer effects of tarragon are based on its antioxidant power and phenolic and flavonoid compounds.

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Introduction

Contemporary medicines have improved the prognosis of cancer patients; however, some cancers do not respond to them [1]. Various studies are being conducted worldwide to find natural chemicals that can suppress or prevent cancer [2-6]. Numerous investigations on the anti-cancer properties of native medicinal plants have also been undertaken in several nations. Plants (fruit, vegetables, and medicinal herbs) are the principal source of natural antioxidants because they contain phenolic compounds, vitamins, and terpenoids [7]. Plant-derived compounds with anti-inflammatory and anti-cancer activities through suppressing the oxidative process have been employed to supplement traditional cancer therapy in recent years [8].

The third leading cause of cancer-related death worldwide is gastric cancer; however, the incidence of gastric cancer varies greatly, and this number can change across populations. Despite many advancements in treatment, those who have undergone surgical procedures have survived less than five years. Even though there are various treatment options for localized gastric cancer, from minimally invasive EMR to aggressively extended lymphadenectomy and perioperative empirical adjuvant chemoradiation, gastric cancer remains a significant clinical challenge. Because most diseases are discovered at a late stage when treatment options are limited, and patients have a median survival of only 6-9 months [9, 10].

Chemotherapy is a common treatment for breast cancer [11], but it is associated with side effects and even irreversible tissue damage in healthy organs due to the selectivity of the drugs used [12]; additionally, drug resistance during the treatment process leads to a poor prognosis [12, 13]. As a result, developing new herbal substances with lower toxicity and adverse effects is an important research area [14]. Natural goods, particularly flowers and plants, have been utilized to treat various ailments throughout history. Natural drug alternatives have been increasingly popular in recent years due to the adverse side effects of many chemical drugs [15].

A variety of herbal remedies have been shown to have anti-cancer properties. Due to the lack of scientific information on the activation pathways of herbal medications, their clinical use has been reduced [16, 17].

Tarragon (*Artemisia dracunculus* L.), a member of the Asteraceae family with an extensive global distribution and several nutritional applications, is effective in various maladies and diseases [18]. With the Mongol invasion, tarragon became the main birthplace of Russia's southern plains and Mongolian and Siberian plains, which expanded to the Middle East and Europe [19, 20].

Estragole (anethole isomers), pinene, camphene, sabinene, myrcene, flandren, limonene, linalool, delta-4-carene, α-flandren, and cis- and trans-ocimene are among the most prominent constituents in tarragon Arial parts [21].

Plant polyphenols are natural compounds utilized as a primary antioxidant and anti-cancer component [22]. According to chemical investigations, coumarins, flavonoids, and phenolic acids are the primary metabolic ingredients of *A. dracunculus* L. Coumarins, such as herniarin, coumarin, esculetin, and esculin are found mainly in the aerial tissues of *A. dracunculus* L. In addition, flavonoids and phenolic acids, such as quercetin, luteolin, naringenin, chlorogenic acid, caffeic acid, caffeoylquinic acid, and chicoric acid have been documented in several investigations. As a result, *A. dracunculus* L. is a rich source of phenolic compounds that can be utilized to preserve foods and contribute to a healthy diet. The antioxidant activity and phenolic content of the tarragon extract were both high. The high free-radical scavenging activity is attributed to its high total phenolic and flavonoid contents. Although the mutagenic and hepatotoxic effects of estragole in high doses of tarragon may pose health problems, the amount of this potentially dangerous chemical in tarragon extracts is low [23]. The ability of *A. dracunculus* L. extracts to decrease malondialdehyde and sialic acid accumulation shows that they can inhibit lipid peroxidation, demonstrating antioxidant potential [19].

The increase in cancer treatment success rates due to the use of alternative therapies that harness the power of plants has prompted scientists to look to natural sources to combat cancer's harmful impacts on life. Plants with physiologically active chemicals make up most of these natural resources [24]. Recent research has looked into the anti-cancer properties of plant-based cancer treatments. Many countries worldwide have researched plant-derived natural chemicals that can be utilized to fight cancer [25, 26]. On average, these natural chemicals are 20 times less harmful than chemotherapy medications [27]. As a result, numerous plants' antioxidant and anti-cancer characteristics have been studied to treat various disorders, especially cancer [28]. *A. dracunculus* L. has essential ethnopharmacological qualities. A literature review revealed no previous relevant study in this regard. The antioxidant, cytotoxic, and genotoxic ef-

fects on the colon (HT29) and breast (MCF7) cancer cells were investigated using the phenolic composition of the hydroalcoholic extract obtained from the above-ground portion of the tarragon, as well as the antioxidant and cytotoxic effects on gastric cancer (MKN45) cells [29].

This study aimed to investigate the cytotoxicity of this plant on different categories of cancer cells ((HT29-HTB-38) and breast cancer (MCF7-HTB-22), and gastric cancer (MKN45-CVCL_0434) cells using by MTT test and evaluated the IC50 value. The antioxidant properties of the extract were also investigated.

Material and Methods

Extraction

The plant leaves were collected from local markets in Sari (Mazandaran province; Herbarium number: 1033). The plant was dried at room temperature, and then grind, and after extraction by soaking it several times, it was extracted four times with the help of 80% methanol. The oil and wax contents of the extract were removed with a hexane solution. Finally, the weight of the dry extract was 12.9 g with a yield of 22.25%.

Determining the flavonoid content of tarragon

The total flavonoid content was determined by spectrophotometric method and aluminum chloride. The quercetin standard with different concentrations of 25, 50, 100, and 200 µg/L was used to draw the calibration curve. Flavonoid content was expressed based on mg quercetin per gram of dry plant extract. In a 10 mL flask, we added 3 mL of distilled water to 1 mL of the sample (different concentrations of extract or standard) and then 0.3 mL of 5% sodium nitrite solution and mixed, and after 5 minutes, 10 mL of aluminum chloride 10% was added and mixed. After 6 minutes, 2 mL of 1 Molar sodium hydroxide was added, and then with distilled water, the final volume reached 10 mL. After mixing at room temperature, it was maintained for 20-30 minutes and the absorbance of the sample read at 510 nm [30].

Determining the total phenol content of tarragon

Total phenolic content was measured based on mg of glycolic acid per gram of dry plant extract. It was determined by spectrophotometry and with Folin–Ciocalteu reagent. Accordingly, 0.5 cc of standard and extract concentrations were poured into the test tube and mixed with 2.5 cc of Folin's reagent. After 10 minutes, 2 cc of 7.5% sodium carbonate solution was added, and the prepared solution was placed in the dark for 60 minutes. Finally, the absorbance of the samples was read using a spectrophotometer at a wavelength of 765 nm. Concentrations of 200, 100, 50, 25, and 12.5 µg of gallic acid were prepared to examine the standard sample [30].

Determination of antioxidant activity by the DPPH method

DPPH (2,2-diphenyl-1-picrylhydrazyl) is a stable free radical that can accept an electron or hydrogen radical and become a stable, neutral molecule. Due to the presence of a single electron, it has strong absorption in the region of 517 nm. As soon as being in the presence of antioxidants, a single electron becomes a pair of electrons. Absorption relative to the received electron decreases in a concentration-dependent manner. DPPH and adsorption reduction occur at 517 nm at room temperature (25°C) and 5 minutes after the reaction. The ability of different molecules as radical scavengers can be measured using the adsorption change in this reaction.

The extract was made with 100, 200, 300, 400, and 500 mg/mL concentrations. Then, various concentrations of vitamin C (4, 8, 12, 16, and 20 mg/mL) were prepared. To prepare DPPH with a 40 mg/mL concentration, 80 mg of this substance reached 100 volumes with methanol. Then, 2 mL of each extract (with different concentrations) was added to 2 mL of methanolic solution of DPPH (100 µM). After 15 minutes at room temperature in the dark, the absorbance was read at 517 nm [30].

Determination of antioxidant activity by ferric reducing antioxidant power (FRAP) method

We added 1.5 mL of the prepared FRAP reagent to the test tube and it was kept for 5 minutes at 37°C. Then, 50 µL of the sample from each standard with different concentrations (1000, 750, 500, 250, and 125 µM ferrous sulfate) was added to the relevant tubes and kept at 37°C for 10 minutes. The color intensity was then read at 593 nm vs. Blanc. Based on different standard concentrations, the amount of optical density or absorbance was read, the standard curve was drawn, and the extract samples' concentration values were calculated from the curve [31].

Evaluation of cytotoxicity

MCF7, MKN45, and Ht-29 were purchased from the Pasteur Institute of Iran. The cells were suspended in a DMEM medium containing 10% FBS and 1% antibiotic and then placed in an incubator until the cells reached

their logarithmic growth stage and were ready for testing. After cell passage, the cells were implanted in 96-well plates and incubated for 24 hours.

MTT colorimetric method was used to evaluate the effect of tarragon extract on the growth and proliferation of cancer cells. This method is a competitive mitochondrial metabolic test, based on the breakdown of tetrazolium salt by the enzyme mitochondrial succinate dehydrogenase of living cells. This method used three cell lines MCF7, MKN45, and Ht-29. 100 µL of cast medium containing 10^4 cells was placed in each 96-well plate well. After 24 hours of incubation, concentrations of 100, 200, 500, and 1000 µg/mL of tarragon extract and Cisplatin (40 µM) as positive control were added to the cells and incubated for 48 hours. Then, 20 µL of MTT was added to each well and incubated in the dark for another 4 hours. The culture medium containing MTT was carefully removed, and 50 µL of diluted DMSO solution was added to each plate to dissolve the purple molds. After 15 minutes of incubation at room temperature, the light absorption of each well was read using ELISA at 490 and 630 nm. The results are reported as a percentage of cell survival against the concentration of the extract [32, 33].

Statistical method

All statistical calculations were performed using Prism software, version 3, using the nonlinear regression method, and the data were compared with ANOVA and Tukey-Kramer multiple comprehension test. Graphs were drawn by the same graphics program.

Results

Total flavonoid content of tarragon extract

Total flavonoid levels of different concentrations of quercetin are reported in Table 1. The total flavonoid content of tarragon hydroalcoholic extract was equal to 24±1.18 mg in terms of quercetin per gram of extract.

Total phenolic content of tarragon extract

Total phenolic levels of different concentrations of gallic acid are reported in Table 2. The total phenolic content of tarragon hydroalcoholic extract was equal to 59±2.21 mg of gallic acid per gram of extract

Antioxidant activity by the DPPH method

The DPPH free radical scavenging method is used to evaluate adsorption reduction activities, resulting in a change in solution color from purple to yellow. The observed discoloration is due to the inhibition of free radical DPPH by the antioxidants present in the sample. By donating hydrogen atoms to the free radical DPPH, the extracts convert it to a stable form of HDPPH, changing the color of the DPPH solution from purple to yellow, thus demonstrating their ability to inhibit free radicals. The concentration of 627.47 µg/mL of tarragon hydroalcoholic extract had a 50% inhibitory effect, and this amount was equal to 13.19 µg/mL for vitamin C.

Antioxidant activity by FRAP method

The antioxidant activity of the hydroalcoholic extract of tarragon was evaluated by the FRAP method in terms of mM iron sulfate. According to the standard curve, the amount of iron reduced by tarragon hydroalcoholic extract was equal to 405±0.11 µg/mL, which can reduce ferrous equivalent to 1 mM of ferrous sulfate (Table 3).

Anti-cancer effects of tarragon hydroalcoholic extract on HT 29 and MCf7 cancer cell lines

According to Table 1, the MTT test showed that tarragon extract had a cytotoxic effect on three cancer cell lines and inhibited cancer cell growth in different concentrations (Table 4).

Moreover, it can be predicted to have the best effect at 500 and 1000 µg/mL concentrations. According to Table 1, the extract at concentrations of 500 and 1000 µg/mL in MCF-7 cells 26.2%, 47.2%, in MKN45 cell line, 28% and 57.4%, and in HT29 cell line, 43.8% and 60.2% inhibited cancer growth.

In the HT-29 cell line, all groups except the 100 µg/mL group, and in comparison with the cisplatin group, all groups except the 500 µg/mL group, had significant differences (Figure 1).

In the MKN45 cell line, only 100 µg/mL was not significantly different from the control group, and 1000 µg/mL was not significantly different from the positive control group (Figure 2).

Also, statistical analyzes of MCF-7 cells showed that in comparison with the control group, concentrations of 500 and 1000 µg/mL ($P<0.01$) and in comparison with the cisplatin group, all groups had significant differences (Figure 3). Table 5 shows the IC50 value of each cell line.

Table 1. Total flavonoid levels of different concentrations of quercetin

Standard Concentrations (µg/mL)	Mean±SD
6.25	0.049±0.005
12.5	0.066±0.001
25	0.094±0.001
50	0.139±0.005
100	0.177±0.001
200	0.259±0.000

PBR

Table 2. Absorption rate of different concentrations of gallic acid to determine the total phenolic content

Standard Concentrations (µg/mL)	Mean±SD
12.5	0.214±0.003
25	0.242±0.003
50	0.278±0.001
100	0.336±0.002
200	0.453±0.002

PBR

Table 3. Absorption rate of different concentrations of ferrous sulfate by FRAP antioxidant method

Standard Concentrations (µg/mL)	Mean±SD
125	0.118±0.004
250	0.172±0.001
500	0.217±0.002
750	0.247±0.002
1000	0.258±0.000

PBR

Table 4. Mean of different concentrations of extract in HT29-MCF7- MKN45 cell line

Cell Line	Mean±SD Concentrations (µg/mL)					
	Control	Cisplatin	100	200	500	1000
MCF-7	96.80±3.96	37.00±4.52	93.80±2.58	86.00±3.93	73.80±3.76	52.80±5.40
MKN45	93.20±2.58	48.00±8.45	89.40±4.50	84.60±4.15	72.00±2.55	42.60±4.21
HT-29	92.20±4.97	52.80±6.01	87.00±5.87	76.80±5.80	56.20±4.81	39.80±3.70

PBR

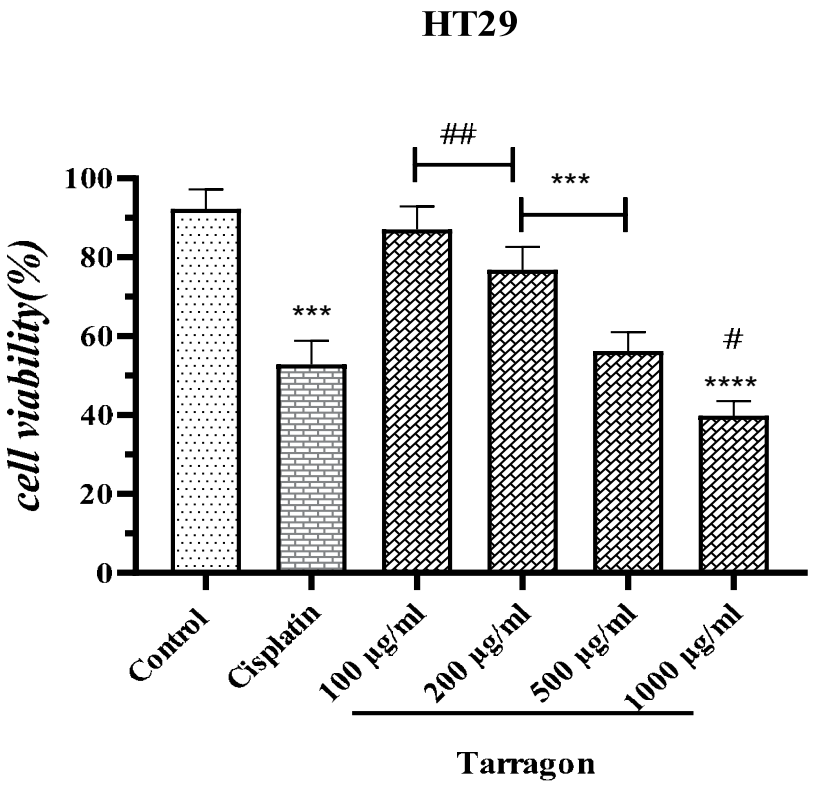

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Figure 1. Cytotoxic effect of Tarragon on HT29 cell linel

***P<0.001, ****P<0.0001 compared to the control group. #P<0.05, ## P<0.01, compared to the cisplatin group.

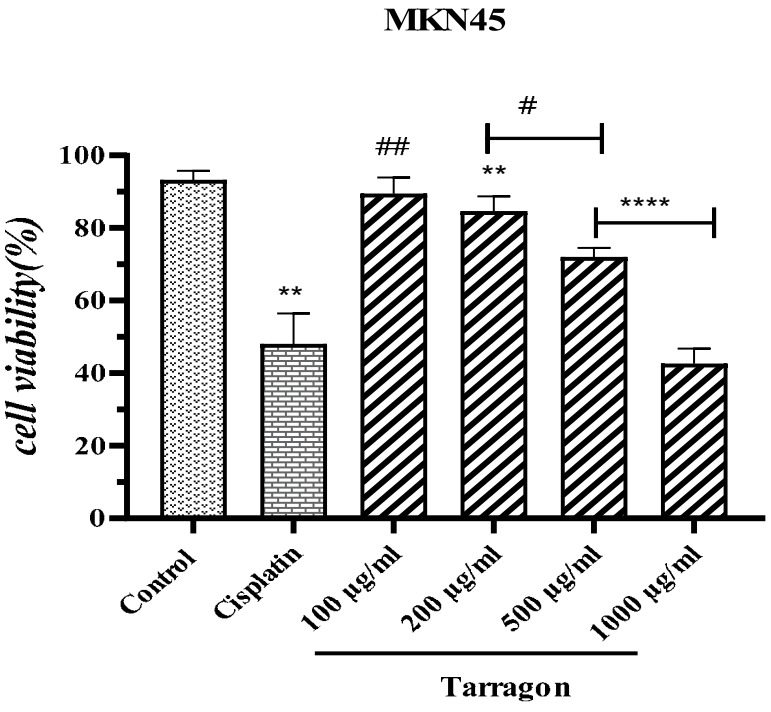

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Figure 2. Cytotoxic effect of Tarragon on MKN45 cell line

**P<0. 01, ****P<0.0001 compared to the control group. #P<0.05, ## P<0.01, compared to the cisplatin group.

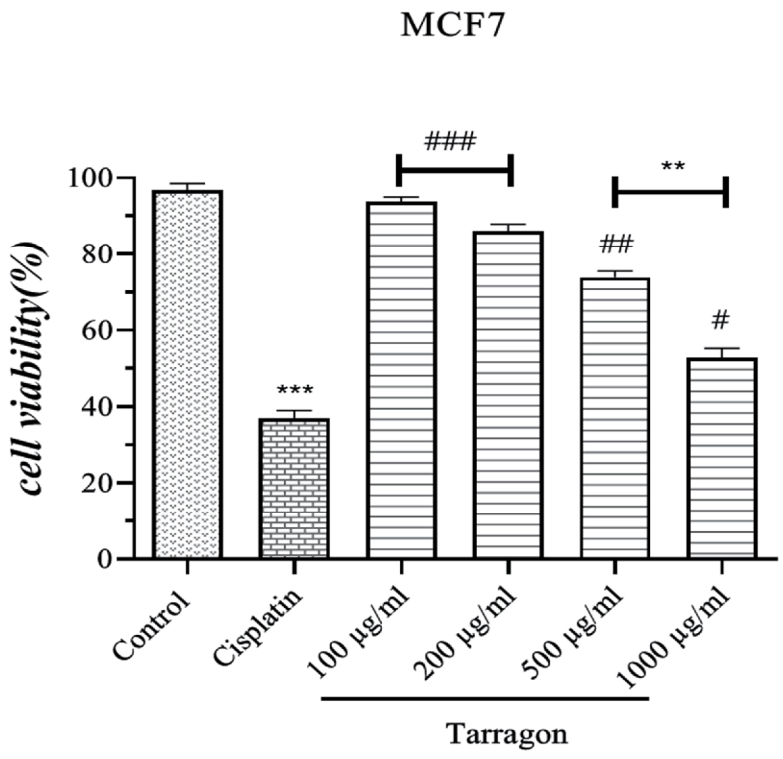

Figure 3. Cytotoxic effect of Tarragon on MCF7 cell line
***P<0.001, **P<0.01 compared to the control group. #P<0.05, ## P<0.01, ###P<0.001 compared to the cisplatin group.

Table 5. IC50 value of extract in HT29-MCF7- MKN45 cell line

Cell Line	LC50 µg/mL
MCF-7	1065.669
MKN45	881.1926
HT-29	743.870

Discussion

A. dracunculus L. (tarragon) belongs to the Asteraceae family and 200–400 species of this genus exist worldwide, depending on the type of climate. Monoterpenes and sesquiterpenes cause a specific odor, which is why this plant is utilized in traditional medicine. Artemisia and its components have been proven to have antimalaria, antioxidant, cytotoxic, antispasmodic, anthelmintic, neuroprotective, anti-inflammatory, and antimicrobial properties [34].

Antioxidant compounds, including phenolic compounds (phenolic acid and flavonoids), are abundant in plants. These compounds have a variety of biological activities, including the prevention of cancer and degenerative diseases [30]. However, all extracts had a high level of antioxidant capabilities, with significantly varying degrees. The Birjand and Varamin accessions have the highest and the lowest capacities, respectively. There were varying levels of total phenolic and flavonoid amounts among tarragon accessions. There was a positive direct correlation between total antioxidant capacities (DPPH and FRAP assays), total phenolic, and flavonoid contents. It demonstrated that phenolic compounds were the primary antioxidant in the assessed plant extracts. Therefore, Tarragon can be considered a credible source of natural antioxidants and is likely to become a valued dietary supplement [23].

In the present study, the extracts showed a concentration-dependent radical inhibitory activity by radical in-

hibition of DPPH. To evaluate the antioxidant capacity of an extract, the activity of the DPPH free radical scavenger represents a widely accepted method. Substances that can perform this reaction can be considered antioxidants. In reducing power, the presence of reductants (antioxidants) in the samples can reduce Fe^{3+} to Fe^{2+} ions. Depending on the amount of antioxidants in an extract, iron depletion is an indicator of electron donor activity, an essential mechanism of phenolic antioxidant function. *A. dracunculus* L. has a 50% inhibitory effect, equal to 13.19 µg/mL for vitamin C, and the amount of iron reduced by tarragon hydroalcoholic extract is equal to 405±0.11 µg/mL.

A. dracunculus L.in the form of a hydroalcoholic extract, showed hepatoprotective properties when dealing with CCl4-induced hepatic damage in rats, suggesting that these effects may be produced by reducing oxidative stress [35]. The methanol extract demonstrated the highest antioxidant activity in all examinations and was a strong foundation of antioxidants with high levels of polyphenolic content [36]. Tarragon extract showed anti-colitis properties in battling cytomegalovirus colitis caused in Wistar rats and can be considered a possible candidate for reducing inflammatory mediators in cancer [37]. In another study, tarragon extracted with 80% methanol displayed dose-dependent effects on mice's spleen and bone marrow mitotic index. The extract increased cell reproduction and the mitotic index at lower concentrations (which in our study, refers to a dose of 500 mg/kg). In contrast, at higher concentrations, like 1000 mg/Kg, the extract displayed anti-proliferative tendencies that could be used in cancer treatment. The anti-proliferative capabilities of *A. dracunculus* have been attributed to its coumarin-like compounds [38].

In addition to its anti-cancer qualities, hydroalcoholic tarragon extracts have shown their ability to increase the proliferation of the innate immune cell's neutrophils. Its immunostimulant quality makes it a viable option for cancer treatment [39]. It can significantly reduce pro-inflammatory IL-17 and IFN-γ cytokines and increase the phagocytosis potential [40]. Isolated elements of *A.dracunculus* have been shown to inhibit cancer cell growth, such as esophageal carcinoma cells, through the induction of cellular apoptosis [41]. The chemical composition of *A. dracunculus* extracts contains essential oils, phenylpropanoids, alkamides, flavonoids, and coumarins. Specific extracts isolated from this herb have hepatoprotective, gastroprotective, and cytotoxic qualities [42]. Compounds with toxic effects, especially cytotoxicity, are candidates for the synthesis of anti-cancer drugs for use in cancer chemotherapy. The present results show that essential oils of mint and tarragon have cytotoxic and anti-proliferative effects on breast cancer cell lines (MCF-7, T-47D, and MDA-MB-231). It can be claimed that the essential oils of both plants have a significant inhibitory effect on breast cancer cell lines. Previous studies on tarragon compounds and GC/mass analysis showed that its essential oil contained 60-70% methyl chavicol (estragole: 66.879%) and some methoxy cinnamaldehyde (bitter substance) [17]. Tarragon extract is cytotoxic for breast cancer by regulating specific proteins that cause apoptosis. Tarragon also contains potent compounds, such as sakuranetin and 6-methoxycapillarysin, which appear to have anti-cancer effects on esophageal cancer by inducing DNA damage in cancer cells [43].

The application of *A. dracunculus* extract reduced autoimmune encephalomyelitis symptoms by inhibiting the production of inflammatory cytokines, including IL-17 and IL-23. The serum antioxidant levels were raised in reaction to the extract [44]. Among the ingredients of tarragon's essential oil, estragole, ocimene, phellandrene, and limonene are proven to have the highest antioxidant qualities. As a result, tarragon essential oil is broadly applied as an antioxidant that could be useful in treating cancer symptoms [45]. Daily supplementation of tarragon increased blood antioxidant parameters of individuals with type 2 diabetes, such as total antioxidant capabilities, glutathione peroxidase, and superoxide dismutase. Therefore, polyphenol antioxidant groups can be crucial in antioxidant modulation [46].

Conclusion

In the present study, and in line with previous studies, the *A. dracunculus* extract inhibited the growth of cancer cells in various cell lines. According to antioxidant tests, it can be said that the anti-cancer effects of tarragon are based on its antioxidant power and phenolic and flavonoid compounds. *A. dracunculus* extract increases the proliferation of neutrophils and inhibits cancer growth.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Research Council of Mazandaran University of Medical Sciences (Code: IR.MAZUMS.RIB.REC.1398.021).

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Authors' contributions

Conceptualization, study design and supervising: Mohammad Shokrzadeh and Emran Habibi; Performing the cytotoxicity experiments, data analysis, drafting the manuscript, reviewing, and editing the article: Farzaneh Motafeghi; Performing the pharmacognosy experiments: Maryam Firozjaei; Contribution in the article writing: Parham Mortazavi, Mohammad Eghbali and Amirhossein Salmanmahiny; All authors read and approved the final manuscript.

Conflict of interest

The authors declared no conflict of interest.

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