Chemical composition and cytotoxic activity of the essential oil from the aerial parts of *Dorema aucheri*

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**Implication for health policy/practice/research/medical education:**
The essential oil of *D. Aucheri* comprised of high amounts of caryophyllene and showed significant cytotoxic effects against SW48 and SW1116 cancerous cell lines. Hence, after more comprehensive studies, it might be used as a beneficial herbal source for developing anti-tumor drugs.

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**Abstract**

**Introduction:** Herbal products are beneficial compounds with many applications in human life. In this study the chemical composition and cytotoxic activity of the essential oil of the aerial parts of *Dorema aucheri* were assessed.

**Methods:** The essential oil was extracted by hydrodistillation after drying the aerial parts of *D. aucheri*, collected from the mountains around Yasuj city in the South-West of Iran. The oil composition was determined by GC/MS. To evaluate in vitro cytotoxic activity, the apoptotic effects of the essential oil were investigated against SW48 and SW1116 colorectal cancer cell lines by (3-[4, 5-dimethylthiazol-2-yl]-2, 5 diphenyl tetrazolium) bromide (MTT) assay and flow cytometry.

**Results:** The essential oil yield was obtained 0.02% (W/W). Twenty-five compounds were identified in the oil, and the main constituents were caryophyllene (E) (31.29%), Phytol (14.92%), gurjunene (β-) (9.84%), 3,7,11,15-tetramethyl-2-hexadecen-1-ol (8.7%), and n-hexadecanoic acid (8.09%). The MTT assay showed that the IC₅₀ values of the essential oil for SW48 and SW1116 cell lines were 1.4 and 1.2 mg/mL, respectively. The results of flow cytometry showed that the essential oil significantly increased the apoptosis in SW48 cell line compared with the vincristine (*P* < 0.05). It also increased the apoptosis in SW1116 cells compared with the vincristine, but this difference is not significant.

**Conclusion:** The essential oil of *D. aucheri* consisted of high amounts of caryophyllene and showed significant cytotoxic effects against SW48 and SW1116 cancerous cell lines.

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**Introduction**

*Dorema aucheri* is a plant of Apiaceae family which grows at the end of the spring in southern provinces of Iran, especially in the provinces bordering the margins of the Zagros mountains, such as Kohgiluyeh and Boyer-Ahmad (1,2). The plant has medicinal properties and also is used by the local inhabitants for preparing food (1,3-5). It has already been proven that the aerial parts of the *D. aucheri* are rich in flavonoids (6). Flavonoids represent a large group of polyphenolic compounds that exhibit anti-oxidative effects (7,8). Although several reports have been conducted on the phytochemistry and
bioactivity of hydroalcoholic extract of \textit{D. aucheri}, the compounds and bioactivity effects of its essential oil have not been clearly determined. Several studies have reported hepatoprotective, anti-diabetic, anti-tumor, anti-oxidant, anti-hyperlipidemic, and anti-hypercholesterolemic effects of the hydroalcoholic extract of this plant (1,3-5,9). Moreover, in several pathological states, it has been reported that \textit{D. aucheri} extract has positive effects on thyroid hormones, antioxidant enzymes, the haematologic system and also serum levels of testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (10). The analysis of essential oil extracted from the leaves of \textit{D. aucheri} showed that it contained 36 (99.86\%) compounds, and the major constituents included curzerene (18.7\%), \textalpha-\text{eudesmol} (7.72\%), Spathululonol (6.68\%), isohibaene (6.16\%), and gemberol (6.66\%) (11). In several studies concerning the extracts of the aerial parts of \textit{D. aucheri}, the presence of a large group of terpenoids, more specifically the sesquiterpene compounds, have been demonstrated. It has been indicated that the pharmacological features of \textit{D. aucheri}, and its potential role in anti-inflammatory, and in the treatment of thyroid disorders and tumors can be due to its sesquiterpene compounds (12). In the present study, the constituents and bioactivity of the essential oil of \textit{D. aucheri} were determined by GC-MS analysis. Also, the cytotoxic effects of these compounds were evaluated against two colorectal cancer cell lines (SW48 and SW1116).

Materials and Methods

Plant materials

The aerial parts of \textit{D. aucheri} were collected from the mountains near the Yasuj city (25 km away from the city, at 30.4658640 N, 51.6783400 E, and the altitude of 2430 m) in Kohgiluyeh and Boyer-Ahmad province, Iran, in the spring of 2017. The plant was authenticated by a botanist (Dr. Azizollah Jafari, a botanist at Yasuj University, faculty of science). The aerial parts were dried in a dark place and then were powdered by an electric grinder. The voucher specimen of the authenticated plant (voucher no. 0496) was deposited at the herbarium of Medicinal Plants Research Center, Yasuj University of Medical Sciences.

Preparation of essential oil

The powder of \textit{D. aucheri} (1200 g) was hydro-distilled in several runs for 4 hours using a Clevenger apparatus. The essential oil was collected, dried with anhydrous sodium sulfate, and kept in refrigerator until GC-MS analysis.

GC-MS analysis and identification of the oil components

The GC-MS analysis of the oil was conducted using a Hewlett-Packard 6890 instrument equipped with a HP-5M capillary column (phenyl methyl siloxane, 25 m x 0.25 mm id, Hewlett–Packard Part No. 190915.433, USA). The oven temperature was adjusted from 50°C (3 minutes) to 250°C at the speed of 3°C min−1 and finally continued for 10 minutes at 250°C. The injection temperature was 250°C. Helium was used as the transferor gas at a constant flow rate of 1.2 mL/min. The mass spectrometer (Hewlett-Packard 5973, USA) was activated in the electron ionization (EI) mode at 70 Ev and the mass range was 30-600 m/z. The identification of components was performed by comparing the relative retention times with those of a series of \textit{n}-alkane standards (C10 to C30: ref. no. R-8769, Sigma) and linear interpolation based on computer matching with the Willey library (Willey-275) and spectra literature data (13).

Cell lines and culturing

Human colorectal cancer cell lines (SW48 and SW1116) were obtained from the Pasteur Institute of Iran. The cell lines were cultured in RPMI-1640 supplemented with 10% fetal calf serum, 1% glutamine, and 100 U/mL penicillin/streptomycin. The cells were cultured in a humidified atmosphere at 37°C and 5% CO₂.

Cell proliferation assay

The cellular proliferation was assessed using MTT (3-[4, 5-dimethylthiazol-2-yl]-2, 5 diphenyl tetrazolium bromide) assay. The cells (5 × 10⁴) were seeded in each well of a microplate, containing 100 μL of the RPMI medium supplemented with 10% FBS. After a 24 hours incubation, the cells were attached to the bottom of each well, and treated with \textit{D. aucheri} essential oil at the concentrations of 0.2 to 1.6 mg/mL for 24 hours. Then, 5 mg/mL MTT reagent was added to each well, and the plate was incubated at 37°C for 4 hours. As the positive control, the cells were treated with vincristine (Sobhan Oncology Co., Iran). Next, the supernatant was removed, and 100 μL DMSO was added to each well. Finally, the optical density of wells was determined at 490 nm using a microplate reader (Stat Fax3200, Awareness Technology, USA).

Apoptosis assay

The SW48 and SW1116 cells (1×10⁶ cells per well) were seeded in six-well plates and then treated with either medium alone (negative control), \textit{D. aucheri} essential oil (1.4 and 1.2 mg/mL), or vincristine (0.05 and 0.04 mg/mL) for 24 hours. The cells were resuspended in a cold binding buffer, then stained with annexin V-FITC reagent (5 μL) and propidium iodide (PI) (5 μL), and incubated in the dark at room temperature for 15 minutes. After adding 500 μL of the binding buffer, fluorescence was read using a fluorescence-activated cell sorter (FACS) (BD Biosciences, San Diego, CA, USA). Flow cytometry data was analyzed by FlowJo software. All the samples were assayed in triplicate.

Statistical analysis

For statistical analysis, the data of cytotoxic activity was compared between different groups by the analysis of
variance (ANOVA) followed by Tukey’s post hoc test. The probability value of *P* < 0.05 was considered to denote a statistically significant difference.

**Results**

The yield of the essential oil extraction was 0.02% (W/W). GC-MS chromatogram of essential oil from the aerial parts of *Dorema aucheri* is shown in Figure 1. The results of GC-MS analysis (Table 1) showed that there were twenty-five (98.39%) known compounds in this essential oil. The main constituents included caryophyllene (*E*) (31.29%), phytol (14.92%), gurjunene (β-) (9.84%), 3,7,11,15-tetramethyl-2-hexadecen-1-ol (8.70%), and *n-*hexadecanoic acid (8.09%).

**Cytotoxic activity**

MTT assay was used to determine the IC_{50} of *D. aucheri* essential oil on SW48 and SW1116 cell lines. The cells were treated with 0.2 to 1.6 mg/mL concentrations of *D. aucheri* essential oil (Table 2). In parallel, vincristine was used as a positive control. The result showed that the essential oil significantly (*P* < 0.05) inhibited the cell growth of SW48 and SW1116 cell lines. As shown in Table 3, the IC_{50} values (The inhibitory concentrations that could reduce 50% of SW48 and SW1116 cells) were 1.4 and 1.2 mg/mL for essential oil and 0.05 and 0.04 mg/mL for vincristine, respectively. The results showed that the SW1116 cell line was more sensitive than SW48 to *D. aucheri* essential oil. Also, it was shown that the SW48 cell line was more resistant than SW1116 to vincristine.

**Apoptosis**

To explore the mechanism by which *D. aucheri* essential oil might exert its anti-proliferative effects on SW48 and SW1116 cell lines, we assessed apoptosis using Annexin V and PI assay. The respective dot plots of this analysis have been shown in Figure 2. Based on the IC_{50} values, the cells were exposed to the essential oil for 24 hours to stimulate apoptosis. Flow cytometry results indicated that, 24 hours incubation with the essential oil significantly elevated apoptosis in SW48 cell line, compared with the vincristine (*P* < 0.05). It also increased the rate of apoptosis in SW1116 cells compared with the vincristine, but this difference was not significant (Figure 3). The apoptosis rates in SW48 and SW1116 cell lines treated with *D. aucheri* essential oil were 14.93% and 7.1%, while the cells treated with vincristine showed 4.5% and 6.43% apoptosis rates, respectively. Also, the essential oil treatment significantly elevated apoptosis in SW48 and SW1116 cell lines, compared with the negative control (*P* < 0.05). The comparison of apoptosis rates between SW48 and SW1116 cell lines showed that *D. aucheri* essential oil induced a significantly higher apoptosis rate in the SW48 cell line.

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**Table 1. List of the components of the essential oil of *Dorema aucheri***

| Compound | Essential oil% | Kovats indices (K.I) |
|----------|----------------|---------------------|
| Linalool | 0.37           | 1084                |
| Ylangene | 0.49           | 1367                |
| Caryophyllene (*E*) | 31.29 | 1413                |
| Aromadendrene | 0.94 | 1420                |
| Gurjunene (β-) | 9.84 | 1426                |
| Barbatene (β-) | 0.69 | 1432                |
| Humulene (α-) | 1.30 | 1445                |
| Acordiene (α-) | 0.34 | 1458                |
| Curcumene (α-) | 1.78 | 1468                |
| Selinene (β-) | 1.01 | 1477                |
| Selinene (α-) | 0.74 | 1487                |
| Cuparene | 3.28           | 1490                |
| Curcumene (β-) | 0.47 | 1500                |
| Bazzanene (β) | 0.64 | 1509                |
| Nerolidol (*E*) | 0.57 | 1534                |
| Longipinanol | 0.99 | 1555                |
| Caryophyllene oxide | 2.55 | 1562                |
| Globulol | 0.37           | 1566                |
| Tridecanol (*n*) | 2.82 | 1576                |
| Unknown | 0.94           | 1622                |
| 1,2-Benzene dicarboxylic acid, bis(2-methylpropyl) ester | 2.85 | 1822 |
| Cyclopentadecanolide | 0.55 | 1826 |
| 3,7,11,15-Tetramethyl-2-hexadecen-1-ol | 8.70 | 1836 |
| Unknown | 0.53           | 1877                |
| Ethyl Linoleolate | 2.80 | 1909                |
| *n-*Hexadecanoic acid | 8.09 | 1943                |
| Phytol | 14.92          | 2092                |

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**Figure 1. GC-MS chromatogram of essential oil from the aerial parts of *Dorema aucheri***

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Chemical Composition and cytotoxic activity of *Dorema aucheri*

The current treatments for cancer, such as chemotherapy and radiotherapy, despite having cytotoxic effects against cancer cells, are associated with the side effects on normal proliferating cells. Therefore, it is required to develop alternative therapeutic approaches with the least possible complications (14-16). Among the potential sources for novel therapeutics, medicinal plants can be the most important options due to their anticancer components such as phenolics, glycosides, steroids, flavonoids, and terpenoids (17-19).

Although several studies have been carried out regarding the beneficial health effects of hydroalcoholic extract of the *D. aucheri* (3,4), there is inadequate knowledge about the composition and properties of the essential oil of this plant. In this study GC-MS analysis showed that terpenoids constituted 70.88% of the compounds identified in the investigated oil, among which sesquiterpenes (55.59%), diterpenes (14.29%), and monoterpenes (0.37%) were the predominant terpene compositions. Despite differences in the types of compounds, these compositions demonstrated similar biological functions compared to those of other plant species assessed in prior studies (7,8,20). Asnaashari et al who analyzed the composition of the essential oil of *D. glabrum* roots by GC/MS method showed that the oil was rich in sesquiterpenes and monoterpenes (21). In another study, the major constituents of the essential oil of *D. ammoniacum* collected from the Kellar mountain, were three hydrocarbon monoterpenes, five oxygenated monoterpenes, ten sesquiterpene hydrocarbons, and thirteen oxygenated sesquiterpenes (22). Akbarian et al in their study, conducted on five *D. aucheri* populations in different regions of Iran, showed that β-caryophyllene, thymol, β-gurjunene, carvacrol, and cuparene were the major components (23). In contrast, in the study of Delnavazi et al on *D. glabrum* plant, although the main components were non-terpene compounds (56%), terpenes were also widely found in the plant (24).

In our study, the analysis of essential oil of *D. aucheri*

| Concentration (mg/mL) | Cell viability (%) |
|-----------------------|--------------------|
|                       | SW48              | SW1116             |
| 0.2                   | 92.42              | 91.23              |
| 0.4                   | 90.54              | 89.71              |
| 0.6                   | 88.38              | 85.42              |
| 0.8                   | 75.36              | 67.31              |
| 1                     | 68.39              | 60.03              |
| 1.2                   | 57.43              | 50.44              |
| 1.4                   | 49.27              | 47.12              |
| 1.6                   | 43.64              | 42.81              |

Table 2. Effect of different concentrations of essential oil of *D. aucheri* aerial parts on viability of SW48 and SW1116 cells after 24 hours using MTT assay

| Sample | MTT assay, IC50 (mg/mL) |
|--------|-------------------------|
|        | SW48              | SW1116             |
| Essential oil | 1.4 ± 0.05 | 1.2 ± 0.02 |
| Vincristine  | 0.05 ± 0.001 | 0.04 ± 0.001 |

IC50: The half maximal inhibitory concentration, SW48: Human colorectal cancer cell line, SW1116: Human colorectal cancer cell line, MTT: microculture tetrazolium.

Results are expressed as means ± SD of three independent MTT assay performed in triplicate. Vincristine was tested as positive control.

Table 3. Cytotoxic activity of essential oil from the aerial parts of *D. aucheri*

In our study, the analysis of essential oil of *D. aucheri* cell line (*P* < 0.05).

**Discussion**

The current treatments for cancer, such as chemotherapy and radiotherapy, despite having cytotoxic effects against cancer cells, are associated with the side effects on normal proliferating cells. Therefore, it is required to develop alternative therapeutic approaches with the least possible complications (14-16). Among the potential sources for novel therapeutics, medicinal plants can be the most important options due to their anticancer components such as phenolics, glycosides, steroids, flavonoids, and terpenoids (17-19).

Although several studies have been carried out regarding the beneficial health effects of hydroalcoholic extract of the *D. aucheri* (3,4), there is inadequate knowledge about the composition and properties of the essential oil of this plant. In this study GC-MS analysis showed that terpenoids constituted 70.88% of the compounds identified in the investigated oil, among which sesquiterpenes (55.59%), diterpenes (14.29%), and monoterpenes (0.37%) were the predominant terpene compositions. Despite differences in the types of compounds, these compositions demonstrated similar biological functions compared to those of other plant species assessed in prior studies (7,8,20). Asnaashari et al who analyzed the composition of the essential oil of *D. glabrum* roots by GC/MS method showed that the oil was rich in sesquiterpenes and monoterpenes (21). In another study, the major constituents of the essential oil of *D. ammoniacum* collected from the Kellar mountain, were three hydrocarbon monoterpenes, five oxygenated monoterpenes, ten sesquiterpene hydrocarbons, and thirteen oxygenated sesquiterpenes (22). Akbarian et al in their study, conducted on five *D. aucheri* populations in different regions of Iran, showed that β-caryophyllene, thymol, β-gurjunene, carvacrol, and cuparene were the major components (23). In contrast, in the study of Delnavazi et al on *D. glabrum* plant, although the main components were non-terpene compounds (56%), terpenes were also widely found in the plant (24).

In our study, the analysis of essential oil of *D. aucheri*...
Vincristine
Essential Oil
on blood
revealed a
of 1.2 mg/mL compared to the value of 1.4 mg/mL
collected
Several studies have shown the anti-cancer effects of
major compound (31.29%) of essential oil of

caryophyllene, a type of sesquiterpene, comprised the
and inhibit the differentiation, angiogenesis, invasion, and

terpenoids present anti-cancer and pro-apoptotic effects
that the essential oil constituents of plants such as

have been shown to effectively induce apoptosis in cancerous

low 14.92%. This compound can
be considered a possible candidate for a wide range of
applications in pharmaceutical, food, and biotechnological
industries (37).

Conclusion
The essential oil of D. Aucheri comprised of high amounts
of caryophyllene and showed significant cytotoxic effects
against SW48 and SW1116 cancerous cell lines. Hence,
after more comprehensive studies, it can be used as a
beneficial herbal source for developing anti-tumor drugs.

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from the D. aucheri.

Authors’ contribution
SAH, GGH, FJN, AG, SH and BM contributed in
designing the study, supervising, editing the manuscript
and analyzing the data. GGH, FGH, SRY participated in
the writing process. The final manuscript was read and approved
by all authors.

Conflict of interests
The authors have no conflict of interests to declare.

Ethical considerations
This study was approved by the Ethical Committee of
Yasuj University of Medical Sciences, Yasuj, Iran (ir.yums.
rec.1395.213). Ethical issues (including text plagiarism,
data fabrication and redundant publication) have been

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of alcohol extract of Dorema aucheri on blood
concentration of gonadotropin and androgen hormones

showed that α-eudesmol was absent, while this compound
has been identified in other species of Dorema. In the
analysis of the oil extracted from D. aucheri collected
from the Hazar mountain, the main components were
α-eudesmol (31.2%) and δ-cadinene (10.9%) (25). Also,
the chemical composition of the essential oil from the
stems and seeds of Dorema ammoniacum revealed a
remarkable difference with our study (26). The reason
for the discrepancy between our findings and previous
ones can be due to the different environmental conditions
leading to qualitative and quantitative variations in the
compositions of oils (27).

Because terpenoids have been found to suppress the
growth of a variety of cancer cells, the aim of the present
study was to evaluate the biological effects of the essential
oil of D. aucheri on SW48 and SW1116 colorectal cancer
cell lines (28). The MTT assay was performed to evaluate
in vitro cytotoxic activity of the essential oil against the
cancer cell lines. The results showed that the essential oil of
D. aucheri inhibited the growth of these cells as compared
to vincristine. Our results also showed that the oil extract
had greater toxic effects against the SW1116 cell line with
the IC50 of 1.2 mg/mL compared to the value of 1.4 mg/mL
obtained for the SW48 cell line.

We also evaluated the apoptotic effects of essential oil of
D. aucheri against the mentioned cell lines using Annexin
V and PI assay. The flow cytometry results indicated that
24 hours incubation with the extract significantly elevated
apoptosis in SW48 cell line, compared to vincristine. The
essential oils of D. glabrum and D. ammoniacum have
been shown to effectively induce apoptosis in cancerous
cell lines (29,30). Many studies have also demonstrated
that the essential oil constituents of plants such as
terpenoids present anti-cancer and pro-apoptotic effects
and inhibit the differentiation, angiogenesis, invasion, and
metastasis of tumor cells (28,31,32). In the present study,
caryophyllene, a type of sesquiterpene, comprised the
major compound (31.29%) of essential oil of D. aucheri.
Several studies have shown the anti-cancer effects of

Figure 3. The apoptotic effects of the essential oil of D. aucheri on SW48 and SW1116 cell lines. The data represent mean ± SEM.
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