Phytochemical constituents and biological activities of *Salvia macrosiphon* Boiss.

Majid Balaei-Kahnamoei1, Mahdieh Eftekhari2, Mohammad Reza Shams Ardekani1,5, Tahmineh Akbarzadeh1,5, Mina Saedi4,5, Hossein Jamalifar6, Maliheh Safavi7, Sohrab Sam7, Naghmeh Zhalehjoo8 and Mahnaz Khanavi1,5,9*

**Abstract**

*Salvia macrosiphon* Boiss. is an aromatic perennial herb belonging to the family Lamiaceae. Phytochemical studies and biological activities of this plant have been rarely documented in the literature. The current study aimed to investigate antibacterial and cytotoxic activity of different fractions of aerial parts of *S. macrosiphon*. Also, we tried to isolate and identify cytotoxic compounds from the plant. In this respect, the hydroalcoholic extract of the corresponding parts of the plant was fractionated into four fractions. Then, antibacterial and cytotoxic activity of each fraction were examined. It was found that the chloroform fraction had a good antibacterial activity against gram-positive and gram-negative bacteria. The most potent cytotoxicity was also obtained by the *n*-hexane fraction comparing with etoposide as the reference drug which was selected for the study and characterization of secondary metabolites. Accordingly, 13-epi manoyl oxide (1), 6α-hydroxy-13-epimanoyl oxide (2), 5-hydroxy-7,4'-dimethoxyflavone (3), and β-sitosterol (4) were isolated and evaluated for their cytotoxic activity. Among them, compound 1 revealed significant cytotoxicity against A549, MCF-7, and MDA-MB-231. It merits mentioning that it showed high selectivity index ratio regarding the low cytotoxic effects on Human Dermal Fibroblast which can be considered as a promising anticancer candidate.

**Keywords:** Antibacterial, Cytotoxic, Lamiaceae, *Salvia macrosiphon* Boiss.

**Introduction**

*Salvia* is the largest genus among the Lamiaceae family members and possesses more than 1000 species which are widely distributed around the world. The Iranian flora comprises 61 *Salvia* species, 17 of which are endemic [1]. A number of *Salvia* genus with valuable biological activities are commercially important and used as a flavoring agent in foods, cosmetics, perfumery, and pharmaceutical industries [2, 3]. The name of *Salvia* comes from the Latin word “salvare” meaning “to heal”, endorsing its medical applications for thousands of years [4]. *Salvia* species have been widely used since ancient times for the treatment of different diseases such as colds, bronchitis, tuberculosis, menstrual disorders, and haemorrhage [5]. In this respect, antiproliferative effects of *Salvia* species on human tumor cell lines [6], the efficacy of *S. miltiorrhiza* for the treatment of cardiovascular and cerebrovascular diseases [7], antimicrobial and insecticidal activities of essential oil of Turkish *S. hydrangea* [8], antioxidant, immunomodulatory, antiinflammatory, antimicrobial, and insecticidal activities of *S. mirzayanii* [9], acetylcholine esterase and melanin synthesis inhibitory activities of *S. officinalis* [10], potent cytotoxicity, antioxidant, α-amylase, and α-glucosidase inhibitory activities of essential oil of *S. syriaca* [11], antibacterial activity of *salvia officinalis* against periodontopathogens [12], and antifungal activity of *Salvia desoleana* Atzei & Picci essential
oil [13] have absorbed lots of attention. Furthermore, different components isolated from *Salvia* species have shown desired biological activity, e.g. antioxidant activity of abietane diterpenoids from *Salvia barrelieri* [14], antiprotozoal activity of triterpenoids from *Salvia hydrangea* [15], and cytotoxic activity of diterpenoids isolated from *Salvia hyurgaia* [16].

Herein, focusing on discovering bioactive secondary metabolites from Iranian *Salvia* species [17], we studied the aerial parts of *Salvia macrosiphon* Boiss., Wild sage known as “Marvak” in Persian [18]. The plant is an endemic species growing in the west and center of Iran, and has been used in Iranian traditional medicine as diuretic, carminative and anti-flatulent [19]. Although, *S. macrosiphon* has been commonly used in traditional medicine, a few phytochemical studies have been developed. In this respect, flavonoids and phenolic compounds (e.g. apigenin and luteolin derivatives, and rosmarinic acid), β-sitosterol, and diterpenes (e.g. 13-epi-manoyl oxide) have been isolated and reported [20, 21]. In this work, we evaluated antibacterial and cytotoxic activities of different fractions of the aerial parts of *S. macrosiphon* and focusing on the efficacy of the *n*-hexane fraction, four compounds including diterpenes (1, 2), flavonoid (3), and steroid (4) were isolated and identified which one of them, compound 2 was reported for the first time for this plant (Fig. 1).

**Materials and methods**

**General experimental procedures**

NMR (nuclear magnetic resonance, as $^{13}$C-NMR, $^{1}$H-NMR) spectra were recorded on an Avance III spectrometer (Bruker) operating at 400.20 MHz for $^{1}$H and 100.63 MHz for $^{13}$C. Solvents for the extraction and column chromatography (CC) were of technical grade and redistilled before use. Silica gel for CC (70–230 mesh) and precoated silica gel F254 (20 × 20 cm) plates for TLC, both supplied by the Merck were used. Deuterated solvents (100 atom %D) were from Armar Chemicals. TLC plates were visualized under UV light (254 and 366 nm) and by spraying with 0.5% anisaldehyde in MeOH, followed by heating at 150 °C.

**Chemical and reagents**

3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), Dulbecco’s Modified Eagle’s Medium (DMEM), penicillin–streptomycin, trypsin–EDTA and fetal bovine serum (FBS) were purchased from Gibco BRL (Life Technologies, Paisley, Scotland). Propidium iodide (PI), 4,6-diamidino-2-phenylindole (DAPI), dimethyl sulfoxide (DMSO), acridine orange and ethidium bromide were purchased from Sigma-Aldrich chemical Co. (St. Louis, MO, USA).

**Plant material**

The flowering aerial parts of *Salvia macrosiphon* Boiss. were collected at full flowering stage from Nurabad Mamassani, located in Fars province, Iran, in May 2014. The specimen of the plant was identified and authenticated by Professor G. Amin and deposited at the Herbarium of Faculty of Pharmacy, Tehran University of Medical Sciences (voucher specimen No. 6762-TEH).

**Cytotoxic activity by MTT assay**

Two different human breast cancer cell lines (MCF-7 and MDA-MB-231), lung cancer cell line (A-549) and normal cell (Human Dermal Fibroblast) were purchased from Pasteur Institute of Iran, Tehran, Iran. The medium of RPMI 1640 (PAA, Germany) including sodium bicarbonate and N-hydroxyethylpiperazone-n-2-ethanesulfonic Acid (HEPES, Biosera, England) was used to maintain the cell lines. The medium was enriched with fetal bovine serum (FBS; Gibco, USA) and antibiotics. Then, incubated in air atmosphere enriched 5% CO$_2$ at 37 °C.

![Fig. 1 Structure of isolated compounds from *S. macrosiphon*](image-url)
cytotoxic activity of all fractions and compounds were examined by the MTT (3-[4,5-dimethylthiazole-2-y]-2,5-diphenyltetrazolium bromide) (Sigma-Aldrich, USA) assay.

Antibacterial activity
In vitro antibacterial activity of all fractions was assessed against gram-positive and negative bacteria (Staphylococcus aureus ATCC 6538P and Escherichia coli ATCC 8739). Minimum inhibitory concentration (MIC) was determined by broth micro-dilution method [22]. Serial dilutions of fractions and antimicrobial agents were prepared in 96-well plates by using (Mueller-Hinton Broth) MHB medium. The standard saline solution was prepared to get inoculants turbidity solution equal to 0.5 McFarland standards. The inoculants of the microbial strains were prepared from 20 h bacterial culture that were adjusted to the serially diluted (1:100) using MHB medium just before adding to the serially diluted samples. The plates were incubated for 24 h at 37 °C and MIC values were recorded as the lowest concentrations which could inhibit visible growth of microorganisms. Each experiment was done in triplicate. The ampicillin was used as the standard antibacterial agent.

Extraction and isolation
The air-dried powdered aerial parts of S. macrosiphon (1.8 kg) were crushed and extracted with methanol (8 × 8 L) at room temperature for 7 days. The extract was concentrated under vacuum to afford dark green gummy residue (90.0 g). The crude methanol extract was mixed with water (700 mL) to form a suspension and partitioned successively with n-hexane, chloroform and ethyl acetate to yield n-hexane (40.0 g), chloroform (20.0 g), ethyl acetate (4.0 g) and water soluble (26.0 g) fractions.

The n-hexane fraction (20.0 g) was then loaded on a silica gel column (700 g, 70–230 mesh, 10 × 30 cm) and it components were separated with a gradient mixture of n-hexane and dichloromethane (100:0 to 0:100) as eluent, followed by increasing concentration of acetone (up to 100%) in dichloromethane. The effluents were collected followed by increasing concentration of acetone (up to 0.5 McFarland standard turbidity and were further diluted (1:100) using MHB medium just before adding to the serially diluted samples. The plates were incubated for 24 h at 37 °C and MIC values were recorded as the lowest concentrations which could inhibit visible growth of microorganisms. Each experiment was done in triplicate. The ampicillin was used as the standard antibacterial agent.

Fraction F6 [30 mg, eluted with dichloromethane-petroleum ether (50:50)] was separated over a silica gel CC (50 g, 70–230 mesh, 1.5 × 60 cm) with a gradient mixture of chloroform-acetone (100/0 to 80/20) as eluent, to afford seven subfractions (6a-6 g). Subfraction 6f was further purified by prep. TLC [chloroform-acetone (95:5)] to afford β-sitosterol (4). Fraction F7 [100 mg, eluted with dichloromethane-petroleum ether (60:40)] was subjected to silica gel CC (70 g, 70–230 mesh, 2 × 80 cm) and eluted with chloroform-petroleum ether (70:30) to give apigenin-4',7-dimethylether (3). From fraction F15 [3 g, eluted with dichloromethane-acetone (80:20)], crude crystals were obtained which were recrystallized from chloroform to afford 13-epi manoyl oxide (1). Fraction F17 [200 mg, eluted with dichloromethane-acetone (80:20)] was subjected to silica gel CC (65 g, 70–230 mesh, 2 × 75 cm) with chloroform-acetone (70:30) as eluent and subfractions (17a-17d) were obtained. Subfraction 17b was further purified by prep. TLC [chloroform-acetone (80:20)] to afford 6α-hydroxy-13-epimanoyl oxide (2). Their structure was elucidated by NMR spectroscopy and electrospray ionization mass spectrometry in comparison to the literature for 13-epi manoyl oxide 1 [21], 6α-hydroxy-13-epimanoyl oxide 2 [23], 5-hydroxy-7,4'-dimethoxyflavone 3 [20], and β-Sitosterol 4 [21].

13-Epi manoyl oxide (1)
White amorphous powder (100 mg). mp: 96–98 °C. 1H NMR (CDCl3, 400 MHz): δ = 5.92 (1H, dd, J = 17.3, 10.7 Hz, H-14), 5.20 (1H, dd, J = 17.3, 1.1 Hz, H-15), 4.98 (1H, dd, J = 10.7, 1.1 Hz, H-15), 1.24 (3H, s, Me-16), 1.15 (3H, s, Me-17), 0.86 (3H, s, Me-18), 0.78 (6H, s, Me-19, Me-20). 13C NMR [100 MHz, CDCl3, based on DEPT, HMQC and HMBC experiments]: Table 1. Electron ionization mass spectrometry (EI-MS) 70 eV, m/z: 290 [M]+, 275, 257, 272, 257, 191, 177, 149, 137, 121, 109, 107, 95, 81, 69, 67, 57, 55, 43.

6α-Hydroxy-13-epimanoyl oxide (2)
White amorphous powder (5 mg). mp: 95–98 °C. 1H NMR (CDCl3, 400 MHz): δ = 5.92 (1H, dd, J = 17.4, 10.8 Hz, H-14), 5.19 (1H, dd, J = 17.4, 1.4 Hz, H-15), 5.00 (1H, dd, J = 10.8, 1.4 Hz, H-15), 4.41 (1H, q, J = 3.1 Hz, H-6), 1.34 (3H, s, Me-17), 1.24 (3H, s, Me-16), 1.18 (3H, s, Me-18), 1.17 (3H, s, Me-19), 0.96 (3H, s, Me-20). 13C NMR (100 MHz, CDCl3, based on DEPT, HMQC and HMBC experiments): Table 1. EI-MS 70 eV, m/z: 306 [M]+, 291, 288, 273, 150, 135, 107, 123.

5-Hydroxy-7,4'-dimethoxyflavone (3)
Yellow needles (5 mg). mp: 171–174 °C. 1H NMR (CDCl3, 400 MHz) δ = 12.82 (1H, s, OH-5), 7.84 (2H, d, J = 8.9 Hz, H-2',H-6'), 7.02 (2H, d, J = 8.9 Hz, H-3',H-5'), 6.58 (1H, s, H-3), 6.48 (1H, d, J = 2.3 Hz, H-8), 6.37 (1H, d, J = 2.3 Hz, H-6), 3.90 (3H, s, OMe-7), 3.88 (3H, s, OMe-4'). EI-MS m/z:298 [M]+, 297, 270, 269, 255, 166, 138, 132.
β-Sitosterol (4)
Colorless needles (7 mg). mp: 132–136 °C. 1H NMR (CDCl3, 400 MHz) δ = 5.35 (1H, d, J = 5.1 Hz, H-6), 3.57–3.47 (1H, m, H-3), 1.00 (3H, s, Me-19), 0.92 (3H, d, J = 6.4 Hz, Me-21), 0.79–0.87 (9H, m, Me-26, Me-27, Me-29 ), 0.68 (3H, s, Me-18). 13C NMR (100 MHz, CDCl3, based on DEPT, HMQC and HMBC experiments): Table 1. EI-MS m/z :414 [M]+, 396, 381, 329, 303, 273, 255, 231, 213.

Results and discussion
Cytotoxic activity
Cancer is the second leading cause of death and responsible for approximately 13% of mortality in the world. The current anti-cancer drugs have shown undesirable side effects, hence, developing novel, efficient, and safe drugs is definitely in high demand [24, 25]. One of the efficient approaches to new drugs is screening herbal extracts [26]. In the present study, S. macrosiphon was selected for the possible cytotoxic activity. For this purpose, different fractions of aerial parts of the plants including n-hexane, chloroform, ethyl acetate, and water-soluble fractions were screened towards lung cancer cell line (A549) and breast cancer cell lines (MCF-7 and MDA-MB-231) as well as normal cell, human dermal fibroblasts (HDF), using MTT assay comparing with etoposide as a standard drug (Table 2). The inhibitory concentration, 50% (IC50) values (µg /mL) were calculated by linear regression analysis, expressed in mean ± SD.

According to calculated IC50 values reported in Table 2, n-hexane and chloroform fractions depicted much higher cytotoxicity than ethyl acetate and water-soluble fractions. However, n-hexane fraction was found to be more potent than chloroform fraction in such a manner that it showed IC50 = 20.89, 10.24, 20.98, and 26.90 µg/mL against A549, MCF-7, MDA-MB-231, and HDF, respectively. Although the cytotoxic activity of n-hexane fraction towards A549 was a little lower than etoposide on the same cell line (IC50 = 16.58 µg/mL), its activity towards MDA-MB-231 (IC50 = 20.30 µg/mL) was as the same as etoposide (IC50 = 20.98 µg/mL). It merits mentioning that cytotoxicity of n-hexane fraction against MCF-7 (IC50 = 10.24 µg/mL) was significantly higher than etoposide (IC50 = 22.08 µg/mL). Apart from high cytotoxicity against MCF-7, the higher the selectivity index (SI) ratio (2.6) was calculated comparing with those obtained for A549 and MDA-MB-231. SI indicates the cytotoxic selectivity for an agent against cancer cells versus normal cell. The greater the SI value is, the more toxic the agent is against cancerous cells but safe against HF [27].

With these results in hand, the n-hexane fraction was candidate for further phytochemical analysis leading to isolation and identification of compounds 1–4. It worth mentioning that there is no report for the cytotoxicity

Table 1 13C NMR of compound 1, 2 and 4, based on DEPT, HMQC, HMBC experiments

| Position | 1  | 2  | 4  |
|----------|----|----|----|
|          | δC (ppm) | δC (ppm) | δC (ppm) |
| 1        | 39.2 | 41.9 | 37.3 |
| 2        | 18.9 | 19.1 | 31.7 |
| 3        | 42.0 | 44.0 | 71.8 |
| 4        | 33.2 | 33.7 | 42.3 |
| 5        | 56.1 | 57.1 | 140.8 |
| 6        | 20.4 | 67.2 | 121.7 |
| 7        | 44.9 | 51.1 | 31.6 |
| 8        | 74.7 | 73.3 | 31.9 |
| 9        | 61.7 | 61.9 | 50.1 |
| 10       | 39.6 | 39.4 | 36.5 |
| 11       | 18.4 | 18.3 | 21.1 |
| 12       | 44.9 | 45.4 | 39.8 |
| 13       | 73.3 | 73.2 | 42.2 |
| 14       | 147.6 | 145.1 | 56.8 |
| 15       | 110.7 | 110.4 | 24.3 |
| 16       | 26.2 | 25.8 | 28.3 |
| 17       | 24.1 | 23.9 | 56.1 |
| 18       | 33.2 | 32.4 | 12.0 |
| 19       | 21.5 | 22.8 | 19.4 |
| 20       | 15.4 | 15.8 | 36.1 |
| 21       | 18.8 | 33.9 | 26.1 |
| 22       | 45.8 | 29.1 | 19.0 |
| 23       | 26.1 | 19.8 | 23.1 |
| 24       | 11.8 | 11.8 | 23.1 |

Table 2 In vitro cytotoxic activity of extracts of S. macrosiphon on cancerous cell lines (A549, MCF-7, MDA-MB-231)

| Fractions      | IC50 (µg/mL) | IC50 (µg/mL) | IC50 (µg/mL) | IC50 (µg/mL) |
|----------------|--------------|--------------|--------------|--------------|
|                | A549         | MCF-7        | MDA-MB-231   | HDF          |
| n-Hexane       | 20.89 ± 0.35 | 10.24 ± 0.15 | 20.98 ± 0.25 | 26.90 ± 1.24 |
| Chloroform     | 22.87 ± 2.56 | 11.72 ± 1.56 | 25.67 ± 2.78 | 113.50 ± 5.24 |
| Ethyl          | 169.80 ± 3.56| 76.43 ± 2.78 | 157.00 ± 6.78| 189.50 ± 7.24 |
| acetate        |              |              |              |              |
| Methanol       | 344.96 ± 8.78| 805.34 ± 10.45| 589.00 ± 10.67| > 800        |
| Etoposide      | 16.58 ± 0.78 | 22.08 ± 0.39 | 20.30 ± 0.21 | 92.70 ± 1.20 |
of those compounds except β-Sitosterol which depicted no activity [28]. Cytotoxic evaluation of isolated compounds (Table 3) demonstrated much higher cytotoxicity of 13-epi manoyl oxide (1) against all cancerous cell lines. Compound 1 showed activity against A549, MCF-7, and MDA-MB-231 with IC50s = 19.37, 22.24, and 34.49 µM, respectively. It should be mention that promising safety was obtained in the case of compound 1 and SI ratio was calculated as 17.4, 21.4, and 15.2 on A549, MCF-7, and MDA-MB-231 comparing with etoposide with IC50s = 28.17, 37.51, and 43.49 µM, respectively. It seemed that chloroform and ethyl acetate fractions were more potent than the methanolic extract of the plant against S. aureus and E. coli [29] which showed MIC values of 1 and 0.5 mg/mL, respectively. It seemed that chloroform and ethyl acetate fractions were more potent than the methanolic extract against S. aureus. However, the methanolic extract was more potent than three fractions against E. coli.

**Antibacterial activity**

The antibacterial activity of n-hexane, chloroform, and ethyl acetate fractions of aerial parts of S. macrosiphon was evaluated against gram-positive bacterium (S. aureus) and gram-negative bacterium (E. coli) based on the agar microdilution method (Table 4). It was found that all fractions depicted moderate to good antibacterial activity with minimum inhibitory concentration (MIC) values ranged from 0.61 to 2.5 mg/mL comparing with ampicillin with MIC values of 0.5 and 0.12 µg/mL against S. aureus and E. coli, respectively. Among fractions, the chloroform fraction exhibited more potent activity against both strains (MIC = 0.61 mg/mL) and ethyl acetate fraction showed lower activity than chloroform fraction against both strains (MIC = 0.80 mg/mL).

However, the n-hexane fraction with MIC values of 1.25 and 2.50 mg/mL against S. aureus and E. coli, respectively was the weakest antibacterial fraction.

**Conclusions**

In conclusion, we investigated phytochemical analysis and biological activities of aerial parts S. macrosiphon. Antibacterial evaluation of n-hexane, chloroform, and ethyl acetate fractions of the plant against S. aureus and E. coli indicated good activity with MIC values ranging from 0.61 to 2.5 mg/mL. Further studies were devoted to the investigation of cytotoxic activity. Evaluation of all fractions against A549, MCF-7, and MDA-MB-231 demonstrated very good efficacy of the n-hexane fraction leading to phytochemical analysis and cytotoxic evaluation of this fraction for the first time. Among four isolated compounds (13-epi manoyl oxide 1, 6α-hydroxy-13-epimanoyl oxide 2, 5-hydroxy-7,4′-dimethoxyflavone 3, and β-sitosterol 4); compound 1 was found as effective as etoposide against A549 and MDA-MB-231 and depicted higher activity than the reference drug, against MCF-7. Another good point comes back to the higher SI ratio of compound 1 for all cancerous cell lines and normal cell (HDF) comparing with etoposide verifying its efficacy and safety. It seems that the n-hexane fraction and also chloroform fraction of S. macrosiphon can be considered for comprehensive investigations to provide an herbal anticancer agent.

**Table 3: Cytotoxicity of isolated compounds on cancerous (A549, MCF-7, MDA-MB-231) and normal (HDF) cell lines**

| Compounds | MIC50 values (µM) and selectivity indexa (in parentheses) |
|-----------|----------------------------------------------------------|
|          | A549           | MCF-7           | MDA-MB-231       | HDF            |
| 1         | 19.37±1.96     | 15.79±0.35     | 22.24±1.72       | 337.58±9.20   |
|           | (17.4)         | (21.4)         | (15.2)           |                |
| 2         | 170.03±11.63   | 98.03±11.27    | 119.51±5.09      | > 653          |
| 3         | 469.23±22.75   | 428.05±23.12   | 469.80±23.12     | > 971          |
| 4         | > 100          | > 100          | > 100            | nd             |
| Etoposide | 28.17±1.32     | 37.51±0.66     | 34.49±0.36       | 157.50±2.04   |
|           | (5.6)          | (4.2)          | (4.6)            |                |

The selectivity index was determined as IC50 value for human normal fibroblast (HDF)/IC50 for cancerous cell line. 

**Table 4: Minimum inhibitory concentration (MIC) of fractions of S. macrosiphon against selected bacteria**

| Microorganism | Fractions (MIC (µg/mL)) | Ampicillin (MIC (µg/mL)) |
|---------------|-------------------------|-------------------------|
|               | n-Hexane | Chloroform | Ethyl acetate | n-Hexane | Chloroform | Ethyl acetate |
| S. aureus     | 1.25     | 0.61       | 0.80         | 0.50     |             |              |
| E. coli       | 2.50     | 0.61       | 0.80         | 0.12     |             |              |

Abbreviations

IC50: the half maximal inhibitory concentration; 1H NMR: Proton nuclear magnetic resonance; 13C NMR: Carbon-13 nuclear magnetic resonance; S. macrosiphon: Salvia macrosiphon; CC: Column Chromatography; TLC: Thin-layer chromatography; DEPT: Distortionless Enhancement by Polarization.
Transfer; HMQC: Heteronuclear multiple quantum correlation; COSY: Correlation spectroscopy; HMBC: Heteronuclear multiple bond correlation; SD: Standard deviation; SI: Selectivity index; UV: Ultraviolet radiation; MeOH: Methanol; MT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; DMEM: Dulbecco’s Modified Eagle’s Medium; FBS: Fetal bovine serum; PI: Propidium iodide; DAPI: 4,6-diamidino-2-phenylindole; DMSO: Dimethyl sulfoxide; MIC: Minimum inhibitory concentration.

Acknowledgements
The authors acknowledged the support from Tehran University of Medical Sciences.

Authors’ contributions
MBK participated in the phytochemical studies, characterization of compounds, and preparation of the manuscript. ME contributed to the selection of the plant for the present study. MRSA and MK supervised all project activities. TA supervised biological activities. MS participated in the characterization of compounds and preparation of the manuscript. HJ conducted the antibacterial assay. MS, SS and NZ participated in assessment of cytotoxic activity. All authors read and approved the final manuscript.

Funding
This work was supported by grants from the Research Council of Tehran University of Medical Sciences with project No. 97-01-33-36289.

Availability of data and materials
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The manuscript does not contain studies with animal subjects.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Department of Pharmacognosy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. 2 Department of Pharmacognosy and Pharmaceutical Biotechnology, School of Pharmacy, Kermanshah University of Medical Sciences, Kermanshah, Iran. 3 Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. 4 Medicinal Plants Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. 5 Persian Medicine and Pharmacy Research Center, Tehran University of Medical Sciences, Tehran, Iran. 6 Quality Control of Pharmaceuticals and Supplements Group, Pharmaceutical Quality Assurance Research Center, The Institute of Pharmaceutical Sciences (TIPS), Tehran University of Medical Sciences, Tehran, Iran. 7 Department of Biotechnology, Iranian Research Organization for Science and Technology, P.O. Box 3353–S111, Tehran, Iran. 8 Department of Biochemistry, Genetics, Nutrition and Medicine, Alborz University of Medical Sciences, Karaj, Iran. 9 Faculty of Land and Food Systems, University of British Columbia, Vancouver, BC, Canada.

Received: 14 October 2020 Accepted: 8 December 2020 Published online: 19 January 2021

References
1. Yi-Bing W, Zhi-Yu N, Qin-Wen S, Mei D, Hiromasa K, Yu-Cheng G, Bin C (2012) Constituents from salvia species and their biological activities. Chem Rev 112:5967–6026
2. Villa C, Trucchi B, Bertoli A, Pistelli L, Parodi A, Bassi AM, Ruffoni B (2009) Salvia somalensis essential oil as a potential cosmetic ingredient. Solvent-free microwave extraction, hydrodistillation, GC-MS analysis, odour evaluation and in vitro cytotoxicity assays. Int J Cosmet Sci 31:53–61
3. Chalchat JC, Michet A, Pasquier B (1998) Study of clones of Salvia officinalis L. yields and chemical composition of essential oil. Flavour Fragr J 13:68–70
4. Minihui L, Qianquan L, Chunzhong Z, Na Z, Zhanhu C, Lucj H, Peigen X (2013) An ethnopharmaceutical investigation of medicinal Salvia plants (Lamiaceae) in China. Acta Pharm Sin B 3:273–280
5. Jash SK, Goral D, Roy R (2016) Salvia genus and triterpenoids. Int J Pharm Sci Res 7:4710
6. Fiore G, Nencini C, Cavalli F, Capasso A, Bader A, Giorgi G, Micheli L (2006) In vitro antiproliferative effect of six Salvia species on human tumor cell lines. Phyther Res 20:701–703
7. Li ZM, Xu SW, Liu PQ (2018) Salvia mitiorrhiza Burg (Danshen): A golden herbal medicine in cardiovascular therapies. Acta Pharmac Sin 39:802–824
8. Kotan R, Kordali S, Cakir A, Kesdeki M (2008) Antimicrobial and insecticidal activities of essential oil isolated from Turkish Salvia hydrangea DC. ex Benth. Biochem Syst Ecol 36:360–366
9. Zarshenas MM, Krenn L (2015) Phytochemical and pharmacological aspects of Salvia mizayyani Rech. f. & Esfand. J Evid Based Complementary Altern Med 20:655–72
10. Sallam A, Mira A, Ashour A, Shimizu K (2016) Acetylcholine esterase inhibitors and melanin synthesis inhibitors from Salvia officinalis. Phytomedicine 23:1005–1011
11. Khodadadi MB, Dinparast L, Zengin G, Sairikucu R, Bahadori S, Ashghar B, Movahedhini N (2017) Functional components, antidiabetic, anti-Alzheimer's disease, and antioxidant activities of Salvia syriaca L. Int J Food Prop 20:1761–1772
12. Mendes F, Garcia LM, Moraes TDS, Casemiro LA, Altacanta CB, Ambrosio SR, Veneziani RCS, Miranda MLD, Martins CHG (2020) Anti-bacterial activity of salvia officinalis L. against periodontopathogens: An in vitro study. Anaerobe 63:102194
13. Sokovic MD, Bricic DM, Dzamic AM, Ristic MS, Marin PD (2009) Chemical composition and antifungal activity of Salvia desoleana Atzei & Picci essential oil and its major components. Flavour Fragr J 24:83–87
14. Kabouche A, Kabouche Z, Ozturk M, Kolak U, Topcu G (2007) Antioxidant abietane diterpenoids from Salvia barrelieri. Food Chem 102:1281–1287
15. Farimani MM, Bahadori MB, Taheri S, Ebrahimi SN, Zimmermann S, Brun R, Amin G, Hamburger M (2011) Triterpenoids with rare carbon skeletons from Salvia hydrangea: Antiprotozoal activity and absolute configurations. J Nat Prod 74:2200–2205
16. Ulubelen A, Topcu G, Chai HB, Pezzuto JM (1999) Cytotoxic activity of diterpenoids isolated from Salvia. hypargenia Pharm Biol 37:148–151
17. Kharomoozeh MM, Tabefam R, Ebrahimi SM, Danton O, Hamburger M, Farimani MM (2019) Chemical constituents from the ethyl acetate extract of salvia hydrangea. Nat Prod Commun 14:1–4
18. Eftekhari M, Shams Ardekani MR, Rafiee Y, Safavi M, Karimpour Razekani E, Khavani M (2011) Biological activities of the essential oil and total extract of Salvia macrosiphon Boiss. J Basic Clin Pharm 8:82–86
19. Hamedi A, Jamshidzadeh A, Ahmadi S, Sohrahbou M, Zarshenas MM (2016) Salvia macrosiphon seeds and seed oil: pharmacognostic, anti-inflammatory and analgesic properties. Int J Pharm 327:27–37
20. Gohari AR, Ebrahimi H, Saeidnia S, Foruzani M, Ebrahimi P, Jafary Y (2011) Flavones and flavone glycosides from salvia macrosiphon bois. Iran J Pharm Res 10:247–251
21. Mattloubi Moghdam F, Moridi Farimani M, Taheri S, Tafazoli M, Amin G (2008) Chemical constituents from Salvia macrosiphon. Chem Nat Compd 44:518–519
22. Kafshgari HS, Yazdanian M, Ranjbar R, Rahimsebi E, Ghazi Miraee SR, Sepahian H, Ebrahimi SM, Goli HR (2017) The effect of Salvia officinalis L on periodontal disease and the antibacterial activity of its essential oil. Lactobacillus acidophilus and Streptococci. J Biol Res 92:30–33
23. Conner AH, Rowe JW (1977) New neutral diterpenes from southern pine tall oil. Phytochemistry 16:1777–1781
24. Remesh A (2012) Toxicities of anticancer drugs and its management. Int J Cancer Res 8:72–86
25. Kroschinsky F, Stolzel F, Bonin SV, Beutel G, Kochanek M, Kehl M, Schel-longowski P (2017) New drugs, new toxicities: Severe side effects of modern targeted and immunotherapy of cancer and their management. Crit Care 21:1–11
26. Vinayak M (2018) Molecular action of herbal antioxidants in regulation of cancer growth: scope for novel anticancer drugs. Nutr Cancer 70:1199–1209
27. Haji Abolhasani M, Safavi M, Goodarzi MT, Kassaei SM, Azin M (2018) Identification and anti-cancer activity in 2D and 3D cell culture evaluation of an Iranian isolated marine microalgae Picoclorum sp. RCC486. DARU. J Pharm Sci 26:105–116
28. Rustaei A, Hadiakhoondi A, Akbarzadeh T, Safavi M, Samadi N, Sabourian R, Khanavi M (2018) Phytochemical Constituents and Biological Activities of Salvia suffruticosa. Res J Pharmacogn 5:25–32
29. Javidnia K, Miri R, Assadollahi M, Gholami M, Ghaderi M (2009) Screening of selected plants growing in Iran for antimicrobial activity. Iran J Sci Technol Trans A Sci 33:329–333

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