RESEARCH ARTICLE

Antimicrobial and cytotoxic activity of extracts from *Salvia tebesana* Bunge and *Salvia sclareopsis* Bornm cultivated in Iran

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Abstract *Salvia*, a member of the Lamiaceae family, represents more than 58 species in Iran. In the present study, antibacterial and cytotoxic activity of extracts obtained from the roots of *Salvia tebesana* and *Salvia sclareopsis* were investigated. The antibacterial activity of the extracts was investigated against 4 bacterial strains and yeast using serial dilution method. The petroleum ether and CH₂Cl₂ extracts of *S. tebesana* showed a good activity against Gram-positive bacteria particularly *Bacillus cereus* (MIC 1.25 mg/mL) while Gram-negative bacteria and yeast were resistant to the extracts. Also, the cytotoxic effects of the extracts on A2780 (ovarian), MCF-7 (breast) and DU 145 (prostate) cancer cell lines were examined using AlamarBlue[®] assay. The petroleum ether and CH₂Cl₂ extracts of *S. tebesana* were found to be cytotoxic against the tested cell lines, with IC₅₀ values less than 50 µg/mL. The petroleum ether extract also showed a potent anti-proliferative activity against DU 145 cells with the lowest IC₅₀ value (6.25 µg/mL).

Keywords *Salvia tebesana* · *Salvia sclareopsis* · Diterpenoids · Antibacterial activity · Cytotoxic assay

Abbreviations

DMSO	Dimethyl sulfoxide
MIC	Minimum inhibitory concentration
MBC	Minimum bactericidal concentration
MHB	Muller Hinton broth
TTC	2,3,5-Triphenyltetrazolium chloride
ROS	Reactive oxygen species
DCFH-DA	Dichloro-dihydro-fluorescein diacetate
DCF	Discounted cash flow

Introduction

Salvia is the largest genus of the Lamiaceae family with about 900 species in the world, of which 58 species are distributed in Iran. Members of this genus produce many useful secondary metabolites including triterpenes, diterpenoids, sesterterpenes, sesquiterpenoids, flavonoids, steroids, caffeoyl derivatives and essential oils. The plants that belong to this genus showed various biological activities such as diuretic, antimicrobial, antifungal, anti-oxidant, antitumor, antidiabetic, anticancer and anti-inflammatory (Duletić-Laušević et al. 2018; Hamidpour et al. 2014; Salari et al. 2016). Traditionally, *Salvia* was used for the treatment of bronchitis, asthma, digestive and circulation disturbances, cough, depression, skin diseases and many other diseases (Khan et al. 2011; Walch et al. 2011).

Salvia tebesana Bunge locally named ‘Maryamgoli Tabasi’ is an endemic plant of Iran that is distributed around Tabas. Recently, the chemical composition of essential oil of *S. tebesana* (7-epi- α -eudesmol, (E)-nerolidol, (E)-caryophyllene, α -pinene, caryophyllene oxide, and δ -cadinen as the main compounds and oxygenated sesquiterpenes and sesquiterpene hydrocarbons were the main group of compound in the oil) (Goldansaz et al. 2017)

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as well as cytotoxic activity of diterpenoids (tebesinone A, tebesinone B, aegyptinone A and aegyptinone B) isolated from root of this species were reported (Eghbaliferiz et al. 2018).

Salvia sclareopsis Bornm, another endemic species of Iran distributed in Ghali kooch of Lorestan Province, is a perennial plant with wooden bin and petiole leaves. Sixteen constituents, representing 96.4% of the total components in the oil of *S. sclareopsis* were characterized by GC–MS and β -caryophyllene, germacrene D and benzyl benzoate have been detected as the main compounds and β -cubebene, α -copaene, 3-isothujopsanone and hexyl benzoate are introduced as other components. Also, sesquiterpenes comprised 74.3%, while the monoterpene fraction was relatively small, representing only 2.6% of the total oil (Jamzad et al. 2009).

Since antibiotic resistance remains an essential driving force to discover new natural antimicrobials, natural compounds are specially being screened for their antimicrobial effect (Shakeri et al. 2018b; Soltanian et al. 2016). Also, the increasing popular concern about the food safety and chemical preservatives caused special attention to antimicrobial potential of natural products (Soltanian et al. 2016). In fact, natural products are commonly supposed to be safer than chemical compounds due to their inherent biocompatibility and biodegradability (Shakeri et al. 2018a). Therefore, many investigations have been published about the potential antimicrobial activity of naturally occurring compounds (Asili et al. 2008; SalarBashi et al. 2012; Salarbashi et al. 2016; Shakeri et al. 2016, 2017). However, to the best of our knowledge, the cytotoxic and antimicrobial activities of the extract from *S. tebesana* and *S. sclareopsis* have not been investigated. Therefore, the present study aimed to investigate the antimicrobial (against both Gram-positive and Gram-negative strains), and cytotoxic (against MCF7, DU 145 and A2780 cell lines) properties of the extract obtained from the root of *S. tebesana* and *S. sclareopsis*.

Materials and methods

Plant material

The roots of plant were collected from the natural localities (*S. tebesana* from its natural habitat near Tabas, South Khorasan Province; *S. sclareopsis* from Ghali kooch, Lorestan Province) in April 2017. The plants were identified by Mr. M.R. Joharchi, from the Ferdowsi University of Mashhad Herbarium (FUMH) and specimen of these plants was deposited in the herbarium of School of Pharmacy, Mashhad University of Medical Sciences.

Preparation of plant extracts

The dried roots of plants were macerated with MeOH, three times (each 24 h) at room temperature. The MeOH extract was filtered and the solvent was evaporated under vacuum to afford crude extract [*S. tebesana* (30 g) and *S. sclareopsis* (50 g)]. Methanol extract was further fractionated by solvent–solvent partition to give four different fractions including petroleum ether, dichloromethane (CH₂Cl₂), butanol (*n*-BuOH) and water (H₂O) (Otsuka 2006). The isolated fractions were concentrated in vacuo and stored at + 4 °C for further experiments.

Cytotoxic activity

Cell culture

A2780 (human ovarian carcinoma), MCF-7 (human breast adenocarcinoma) and DU 145 (prostate cancer) cells were provided by the Biotechnology Research Center (Mashhad, Iran). Cell lines were maintained in RPMI 1640 supplemented with 10% fetal bovine serum and antibiotics (100 mg/mL penicillin/streptomycin). Cultures were incubated at 37 °C in an atmosphere of 95% O₂ and 5% CO₂.

Cell viability assay

Cytotoxicity was evaluated using a non-fluorescent substrate, AlamarBlue®, based on the reduction of resazurin to resorufin (O'Brien et al. 2000). Briefly, A2780, MCF7 and DU 145 cells were plated at a density of 10⁴ cells (100 μ L/well) into 96-well plates under humidified atmosphere at 37 °C with 5% CO₂. After an overnight incubation at 37 °C to allow cell attachment, extract was dissolved in DMSO (0.5%), and then diluted in RPMI medium for use. The extract concentrations (2.5 to 50 μ g/mL) were added to seeded wells in triplicate and incubated for 48 h. Then 20 μ L of AlamarBlue® reagent was added to the attached cells. After 4 h incubation, the absorbance was measured at 600 nm using ELISA microplate reader. Doxorubicin was used as a positive control. Each experiment was done in triplicate. The percentage viability was determined as formulated below:

$$\text{Viability(\%)} = [(At - Ab)/Ac - Ab] \times 100$$

where At, Ab and Ac is absorption of treated, blank and control wells.

Detection of intracellular reactive oxygen species level

Reactive oxygen species level was measured as described previously with minor modifications (Sharma and Bhat

2009). Cells (1×10^4) were seeded in 96-well plates overnight and then were treated with different concentrations (2.5 to 50 $\mu\text{g/mL}$) of extracts for 24 h. Then cells were incubated with 50 μL H_2O_2 (24 mM) at 37 °C for 30 min. Then 50 μL of DCFH-DA were added to the cells and the fluorescence intensity of DCF was measured at 504 nm emission and 524 nm excitation using a Synergy H4 microplate reader (BioTek, USA).

Determination of antimicrobial activity

Microbial strains and culture media

The extracts from *S. tebesana* and *S. sclareopsis* was tested against two Gram-positive (*Staphylococcus aureus* PTCC 1337 and *Bacillus cereus* PTCC 1241) and two Gram-negative (*Pseudomonas aeruginosa* PTCC 1074 and *Escherichia coli* PTCC 1338) bacteria. *Candida albicans* (PTCC 5027) was employed for anti-fungal activity evaluation. All bacterial strains were cultured overnight at 37 °C on Mueller–Hinton agar (MHA), while *C. albicans* was cultivated 48 h at 25 °C on MHA.

Antibacterial activity

In order to determine MIC (minimum inhibitory concentration) and MBC (minimum bactericidal concentration) values, the stock of extracts were prepared in Muller Hinton broth (MHB) in the presence of 5% DMSO. For the first concentration (80 mg/mL), 320 mg of extract was dissolved to reach the final volume of 4 mL. Other concentrations were prepared serially in sterile condition, using two-fold dilution method by mixing 2 mL of the previous concentration with the same volume of culture broth (2 mL), until reaching the final concentration of 1.25 mg/mL. Then, 180 μL of each extract concentration in a sterile 96-well microtitre plate was inoculated with 20 μL of 10^6 CFU/mL overnight bacterial culture prepared in sterile normal saline (0.9%). All measurements for each bacterium were repeated in duplicate. MHB were used as negative control while the cultured bacteria in MHB were considered as positive controls. After an overnight incubation at 37 °C, the bacterial growth in the wells were determined by adding 20 μL of colorimetric indicator, 2,3,5-triphenyltetrazolium chloride (TTC) (5 mg/mL). Then, the plates were incubated again at 37 °C for 1 h. The MIC was determined as the first concentration with no color alteration to red.

MBC was determined by reculturing 20 μL of extracts from no color changed wells in 180 μL MHB and incubated overnight at 37 °C. The MBC was determined as the lowest concentration without any bacterial growth.

Antifungal activity

The extracts concentrations were prepared according to the previous method in MHB. The fungal cell concentration was provided in sterile normal saline (0.9%) and adjusted to 10^6 CFU/mL. The MIC value was determined in the same volume and concentration as bacterial strains experiment and repeated in duplicate. Positive and negative controls were also included and the plate was incubated at 25 °C for 48 h.

The MIC and MFC (minimum fungicidal concentration) values were determined in the same way as bacterial experiment except the incubation time which was considered as 24 h.

Statistical analysis

The relative results of the experiments were presented as the mean $\pm$ SD of the three independent measurements. Analysis of variance and IC_{50} calculation were performed with GraphPad Prism 6.0 using one-way ANOVA test and the means were compared by Dunnett tests.

Result and discussion

Cytotoxic activity

The cytotoxic activity of different extract from *S. tebesana* and *S. sclareopsis* were studied against cultured A2780 (ovarian), MCF-7 (breast) and DU 145 (prostate) cancer cell lines using AlamarBlue® assay (Table 1). The cells were subjected to increasing doses of the extract ranging from 2.5 to 50 $\mu\text{g/mL}$.

The results showed that *S. tebesana* extracts especially petroleum ether and CH_2Cl_2 exhibited significant cytotoxic activity on cancer cells. Cytotoxic activity of *S. tebesana* against DU 145 cells (IC_{50} : 6.25 $\mu\text{g/mL}$) was significantly stronger compared with other cell lines. Although in this study, extracts of *S. sclareopsis* did not show significant cytotoxic activity on investigated cell line but petroleum ether extract was partially active against cancer cell lines. Extracts with IC_{50} values lower than 50 $\mu\text{g/mL}$ could be considered as promising candidates for development of anticancer agents (Bézivin et al. 2003).

In the present study, DU 145 cells were found to be more sensitive to the cytotoxic effects of the extract compared to MCF-7 and A2780 cells. According to the Eghbaliferiz et al. (2018), the cytotoxicity of *S. tebesana* is related to the presence of abietane diterpenoids in the roots, which may affect through several mechanisms including reduction of the membrane-bound enzymes activity, disruption of cell membrane, increasing the permeability or

Table 1 IC₅₀ values (μg/mL) for different extracts of *S. tebesana* and *S. sclareopsis*

Plant	Cells	Petroleum ether	CH ₂ Cl ₂	MeOH	BuOH	Doxorubicin ^a
<i>S. tebesana</i>	A2780	19.47 ± 1.09	48.24 ± 3.24	> 50	> 50	1.23 ± 0.89
	MCF-7	17.48 ± 0.72	33.98 ± 2.22	46.09 ± 1.68	> 50	2.08 ± 0.25
	DU 145	6.25 ± 2.56	13.68 ± 0.47	24.53 ± 0.65	> 50	1.33 ± 0.72
<i>S. sclareopsis</i>	A2780	45.32 ± 1.19	> 50	> 50	> 50	1.68 ± 0.98
	MCF-7	37.54 ± 1.87	> 50	> 50	> 50	2.25 ± 1.23
	DU 145	28.32 ± 3.25	42.95 ± 1.25	> 50	> 50	1.45 ± 1.36

^aPositive control substance

induction of apoptosis (Elson 1995). In another study, abietane-derivative diterpenoids extracted from *S. lachnostachys* inhibited the growth of six cancer cell line (U251, MCF-7, NCI-ADR/RES, NCI-H460, PC-3 and OVCAR-03) with IC₅₀ 19.9–29.3 μM (Oliveira et al. 2016). Salyunnanins A–F, the main abietane diterpenoids isolated from *S. yunnanensis* showed significant inhibitory activity against six human tumor lines (Wu et al. 2014).

The cytotoxic activity of *Salvia* genus was also studied in other investigations. In a study conducted by Shaheen et al. (2011), the cytotoxic effect of acetone, MeOH and n-BuOH extracts from *S. lanigera* and *S. splendens* were evaluated against selected human tumor cell lines (SNU-398, Hep G2, PLC/PRF/5, A-498, HT-1376, UM-UC-3, Hs 746T, Hs 740.T, Hs 388.T, Hs 751.T, MES-SA and MES-SA/MX) (Shaheen et al. 2011). The acetone extract of *S. lanigera* indicated the highest cytotoxic activity (IC₅₀ values from 9.83 to 100 μg/mL). Also, the water extract of *S. amplexicaulis* and *S. ringens* presented the strongest cytotoxic activity against K562 cells (Alimpic et al. 2015). Moreover, Moradi-Afrapoli et al. reported the abietane diterpenoids isolated from *S. sahendica* had cytotoxicity against cervical (HeLa) and colorectal adenocarcinoma (Caco-2) cancer cell with IC₅₀ 5.4–41.4 μg/mL (Moradi-Afrapoli et al. 2018).

Effect of extracts on ROS formation

The impact of extract from *S. tebesana* and *S. sclareopsis* on ROS production were investigated (Table 2). The obtained results showed that both plant extracts caused a

significant increase in ROS production. After 24 h, *S. sclareopsis* generate high level of ROS, but *S. tebesana* decreased the level of ROS in comparison to the control. Generally, it is believed that abietane diterpenoids in *S. tebesana* are able to scavenge endogenous cellular ROS. Those properties of compounds from *Salvia* extracts may play an important role in cancer therapy by activating apoptotic processes where the basal level of ROS is already decreased. The data suggested that *Salvia* extracts protected cells from ROS and H₂O₂-induced loss of viability damage via activating the cellular antioxidant system. In this paper, *S. tebesana* extracts especially petroleum ether and CH₂Cl₂ significantly decreased the level of ROS and indicated the high cytotoxic activity.

In a study conducted by Jeong et al., baicalein indicated high cytotoxic activity in HEI193 Schwann cell through attenuating H₂O₂-induced apoptosis, eliminating ROS and activation of the Nrf2/HO-1 signaling pathway (Jeong et al. 2019). In another study, *Allium sativum* indicated high cytotoxic activity against SCC-15 cell line and induce apoptosis through the reduction of reactive oxygen species and activation of caspase-3, caspase-8, and caspase-9 in Hep3B cells after 48 h of exposure (Szychowski et al. 2018).

Antibacterial activity

The antibacterial activity of different extracts from *S. tebesana* and *S. sclareopsis* were tested against two Gram-negative and two Gram-positive pathogenic bacteria (Tables 3, 4).

Table 2 Effects of different extracts of *S. tebesana* and *S. sclareopsis* on ROS production (%)

Plant	Cells	Petroleum ether	CH ₂ Cl ₂	MeOH	BuOH	Doxorubicin ^a
<i>S. tebesana</i>	A2780	49.53	78.26	90.36	> 100	100
	MCF-7	35.38	50.12	69.73	91.11	100
	DU 145	26.53	30.78	49.54	70.26	100
<i>S. sclareopsis</i>	A2780	78.56	> 100	> 100	> 100	100
	MCF-7	53.58	> 100	> 100	> 100	100
	DU 145	46.21	68.64	98.19	> 100	100

^aPositive control substance

Table 3 Minimum inhibitory concentrations (MICs) of extracts of *S. tebesana* and *S. sclareopsis* (mg/mL)

Plant	Bacterium	Petroleum ether	CH ₂ Cl ₂	MeOH	BuOH
<i>S. tebesana</i>	<i>Staphylococcus aureus</i>	1.25	1.25	1.25	40
	<i>Bacillus cereus</i>	1.25	1.25	1.25	20
	<i>Pseudomonas aeruginosa</i>	40	20	40	80
	<i>Escherichia coli</i>	80	40	80	80
	<i>Candida albicans</i>	80	40	> 80	> 80
<i>S. sclareopsis</i>	<i>Staphylococcus aureus</i>	80	20	80	80
	<i>Bacillus cereus</i>	80	40	80	80
	<i>Pseudomonas aeruginosa</i>	80	40	80	80
	<i>Escherichia coli</i>	80	40	> 80	> 80
	<i>Candida albicans</i>	80	40	> 80	> 80

Table 4 Minimum bactericidal/fungicidal concentrations (MBCs/MFCs) of extracts of *S. tebesana* and *S. sclareopsis* (mg/mL)

Plant	Bacterium	Petroleum ether	CH ₂ Cl ₂	MeOH	BuOH
<i>S. tebesana</i>	<i>Staphylococcus aureus</i>	–	5	5	–
	<i>Bacillus cereus</i>	–	5	5	–
	<i>Pseudomonas aeruginosa</i>	–	–	–	–
	<i>Escherichia coli</i>	–	–	–	–
	<i>Candida albicans</i>	–	–	–	–
<i>S. sclareopsis</i>	<i>Staphylococcus aureus</i>	–	5	–	–
	<i>Bacillus cereus</i>	–	80	–	–
	<i>Pseudomonas aeruginosa</i>	–	80	–	–
	<i>Escherichia coli</i>	–	80	–	–
	<i>Candida albicans</i>	–	80	–	–

All of the examined extracts inhibited bacterial growth with MIC values ranging from (1.25 to 80 mg/mL). The petroleum ether and CH₂Cl₂ extracts of *S. tebesana* generally showed stronger activity (MICs 1.25–20 mg/mL) than similar extracts of *S. sclareopsis* (MICs 40 to 80 mg/mL). In the present study, Gram-positive bacteria were more sensitive compared to Gram-negative strains. Among the Gram-positive bacteria, *B. cereus* was considerably inhibited by the extracts of *S. tebesana* with MIC of 1.25 mg/mL (except BuOH extract). The high antibacterial activity of *S. tebesana* against gram-positive strains may be related to the presence of abietane diterpenoids in the plant and may act via various mechanisms including impairment of the bacterial enzyme systems, increase of ion permeability and leakage of vital intracellular constituents. The most resistant bacteria to the examined extracts were gram-negatives, which could be attributed to the presence of their outer membrane which act as a barrier towards macromolecules (Shakeri et al. 2014). However, both *S. tebesana* and *S. sclareopsis* extracts had no satisfactory effect against *C. albicans*.

The obtained results are in accordance with previous outcomes related to the antimicrobial effect of genus *Salvia*. For instance, the methanol extract of *S. fruticosa* displayed high activity on Gram-negative bacteria growth

(*Salmonella typhimurium* and *Enterobacter aerogenes*) which may attribute to the significant amount of carvacrol (Askun et al. 2009). In a study conducted by Duletic-Lausevic et al., ethanol extracts of *S. fruticosa* showed stronger activity than *S. lanigera*, particularly against Gram-positive bacteria (Duletic-Laušević et al. 2018). In another study, Hawas et al. showed the ether, chloroform, ethyl acetate, n-butanol, ethanol, and water extracts of *S. lanigera* have high activity against Gram-positive bacteria (Hawas and El-Ansari 2006).

Bisio et al. investigated antimicrobial activity of diterpenoids isolated from *Salvia chamaedryoides* against 26 clinical pathogens. These compounds indicated high activity against Gram-positive staphylococcal and enterococcal species and no activity was detected for the Gram-negative species tested (Bisio et al. 2017). Carnosic acid and carnosol isolated from *Salvia officinalis* were tested against four bacterial strains including *E. coli*, *P. aeruginosa*, *B. subtilis*, and *S. aureus*. The result showed carnosic acid content of 116 µg/mg and a carnosol content of 60.6 µg/mg were found to be the most potent agent against *B. subtilis* (Pavic et al. 2019).

In another study, antibacterial activity of ethyl acetate and ether extracts of *Salvia multicaulis* was investigated. The ether extract showed greatest antimicrobial activity

against *Klebsiella pneumoniae* (10.7 µg/mL) and *Saccharomyces cerevisiae* (10.7 µg/mL) and ethyl acetate extracts showed greatest antimicrobial activity against *B. subtilis* (106.7 µg/mL) and *C. albicans* (5.3 µg/mL) (Taran et al., 2011). Obviously, these antimicrobial effects could be related to the semi-polar contents of the extracts which were in accordance to our findings.

Conclusion

This study determined the biological effects of four extracts (Petroleum ether, CH₂Cl₂, MeOH and BuOH) from *S. tebesana* and *S. sclareopsis*. Among them, the petroleum ether and CH₂Cl₂ extracts of *S. tebesana* showed the strongest activity in the most of the applied antibacterial and cytotoxic assays, while petroleum ether extract of *S. sclareopsis* was only somewhat active against cancer cell lines. However, the petroleum ether and CH₂Cl₂ extract from *S. tebesana* decreased the level of ROS and indicated antioxidant activity. It seems that semi and nonpolar compounds (related to CH₂Cl₂ and petroleum ether fractions respectively) are responsible for both antimicrobial and cytotoxic activity. Considering our previous study, this effect can be attributed to the presence of diterpenoids as the major component of the CH₂Cl₂ extract. The studied *Salvia* species can be interesting to the pharmaceutical industry, and this study will serve as a base for new research on these species.

Future studies are encouraged to find the major components responsible for the observed biological activities of the extracts and their mechanisms.

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Author's contribution S. Eghbaliferiz, V. Soheili, S.A. Emami, M. Iranshahi and Z. Tayarani-Najaran conducted experiments and analyzed data. S. Eghbaliferiz wrote the manuscript. All authors read and approved the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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