Essential Oil of *Salvia officinalis* L. from the Algerian Saharan Atlas: Chemical Composition and Biological Evaluation

Hadjaissa Mahdjoubi[1], Boulanouar Bakchiche[1], Abdelaziz Gherib[1], Fadila Boudjelal[2], Sanaa K. Bardaweel[2*]

[1]Laboratory of Process Engineering, Faculty of Technology, Amar Telidji University Laghouat, Algeria.
[2]Department of Pharmaceutical Sciences, School of Pharmacy, The University of Jordan, Amman 11942, Jordan
*Corresponding author: S.Bardaweel@ju.edu.jo

ABSTRACT

In this study, chemical composition, and biological activities of the essential oil of *Salvia officinalis*, a native plant cultivated in Laghouat (Algerian Sahara), were studied. Chemical composition of the essential oil was identified by gas chromatography/mass spectrometry (GC/MS). Thirty-nine components representing 96.41% of the essential oil were detected with camphor (16.41%), α-thujone (15.68%), manool (15%), viridiflorol (11.69%) and 1,8-cineole (10.06%) as the major compounds. Antioxidant activity was employed by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) free-radical scavenging. The essential oil's IC_{50} value was 0.222 mg /mL in the DPPH assay which could be regarded as reasonable antioxidant power. The antimicrobial activities were evaluated on selected Gam-positive and Gram-negative bacteria, as well as on two pathogenic fungi. The results revealed agreeable and broad-spectrum antibacterial activity while the oil demonstrated weak antifungal potential. On the other hand, the antiproliferative potential of the oil was assessed on different human cancer cell types with the oil's activities on leukemia and prostate cancers being reported for the first time in literature. The LD_{50} values of the oil were in the 200-400 µg/mL on the different cancer types examined. These findings may encourage further investigations in the potential use of *S. officinalis* oil as naturally occurring bioactive ingredient for food and pharmaceutical industry.

Keywords: *Salvia officinalis*, essential oil, chemical composition, antioxidant, antiproliferative, antimicrobial.

1. INTRODUCTION

The family of Lamiaceae consists of about 230 genera and 7100 species worldwide. Many species from the Lamiaceae family are considered of high importance because of their uses in medicine (**1**). The genus Salvia includes approximately 900 species that are widely growing throughout the Mediterranean (**2**). In Algeria, 23 Salvia species are growing, among which *Salvia officinalis* (common sage) is the most common species of the genus (**3,4**).

Salvia officinalis is a perennial round shrub; its leaves and flowering tops have strong aromas and are used to produce essential oils. Compared to other species of Salvia, *S. officinalis* is considered to have the highest abundance of volatile oils (**5**). Since antiquity, this plant has been recognized for its medicinal significance (**6**). It is used in folk medicines for antibacterial, antitumor, antioxidant and anti-inflammatory treatments, as well as for a range of diseases including those of the nervous system, heart and blood circulation, the respiratory, digestive, metabolic, and endocrine system (**7, 8, 9,10,11**).

Phytochemical studies of *Salvia officinalis* revealed a great number of bioactive compounds possessing a variety of biological activities. Interestingly, **S. officinalis** is considered to have the highest amount of essential oil compared to the other species of **Salvia** (**5**). *Salvia*

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officinalis essential oil has various compositions depending on the genetic, climatic, season, and environmental factors (**12**). The purpose of the current study was to identify the chemical composition of the essential oil extracted from *Salvia officinalis* grown in Algeria from the Laghouat region via GC-MS technique and to determine the antioxidant activity along with other biological activities associated with the essential oil.

Materials and Methods

Plant Material

The aerial parts of *S. officinalis* were collected during the flowering stage in July 2016 from the Laghouat region of Algeria (latitude 33°47'59''N longitude 2°51'54''E and altitude 764 m). The plant material was taxonomically identified by the botanical survey, and the voucher specimens (LGP So/07/16) were deposited in the laboratory of Process Engineering, University of Laghouat (Algeria).

Extraction of Essential Oil

The aerial parts (100 g) of *S. officinalis* were subjected to hydrodistillation for 3 h with 500 mL of distilled water using a Clevenger-type apparatus. The prepared volatile oils were dehydrated over anhydrous sodium sulphate and stored in dark vials in refrigerator at 4°C until analyzed. The yield was expressed in percentage.

Essential Oil Gas Chromatography-Mass Spectrometry Analysis

The essential oil analysis was performed on a chromatography's type Hewlett-Packard HP 7890 equipped with a capillary column HP-5MS (30 m × 0.32 mm, i.d., 0.25 µm film thicknesses) coupled to a mass spectrometer (MS) type with a Hewlett Packard 5975 detector impact of electrons, 70 EV. Oven temperature was held at 60°C for 8 min and increased from 60°C to 250°C at a rate of 2°C/min and held at 250°C for 20 min. Injector and detector temperatures were 250 and 280°C, respectively. Carrier gas was nitrogen at a flow rate of 1.2 mL/min in split mode 1:50 with an injection volume of 1 µL. The GC analysis was carried out using an Agilent 6890N GC system equipped with flame ionization detector (FID) operated at a temperature of 280°C. To obtain the same elution order of peaks detected by GC/MS, simultaneous injection on the GC was performed using the same column and appropriate chromatographic conditions as those described for the GC/MS system (**Table1**). Identification of the essential oil components was carried out by comparing their mass spectra and their KI (Kovats Index) with available databases (**13**). The percentage of each compound was computed using normalization method from the GC peak areas, calculated as mean values of three injections, without using correction factors.

Table 1: General information on GC-MS analysis performed.

Column type	HP-5MS (5% Phenyl, 95% dimethylpolysiloxane) 30m*0.32mm*0.25µm
Injection volume	1 µL
Injector tempereture	250 °C
detector temperature	280 °C
Mode of injection	Split 1:50
Vector gas	Helium

Determination of Antioxidant Activity

Radical scavenging activity of *S. officinalis* essential oil against DPPH radical was determined spectrophotometrically (**14**). The scavenging rate on DPPH radicals was calculated according to the formula:

$$Scavenging\ rate\ (\%)=[(A_0-A_1)/A_0]x100\%$$

where A_0 is the absorbance of the control solution, A_1 is the absorbance in the presence of samples in DPPH solution. The scavenging activity of the sample against DPPH radicals was expressed by IC_{50} value, defined as is the effective concentration at which DPPH radicals are scavenged by 50%, and is obtained by interpolation from

regression analysis (**14,15,16**).

Determination of Antimicrobial Activity

Microorganisms

The following microbial strains were obtained from the Microbial Culture Collection Centre of Medicine School at The University of Jordan: *Staphylococcus aureus* ATCC25923 (gram-positive bacterium), *Staphylococcus epidermidis* ATCC 12228 (Gram-positive bacterium), *Escherichia coli* ATCC 29425 (Gram-negative bacterium), *Pseudomonas aeruginosa* ATCC 15442 (Gram-negative bacterium), *Candida glabrata* ATCC 22553 (fungus), and *Candida albicans* ATCC10231 (fungus). The bacteria species were maintained in Mueller Hinton Agar and Triptic Soy Agar (MHA, TSA, Merck, Germany) whereas *Candida* spp. were maintained on Sabourand Dextrose Agar (SDA, Merck, Germany).

Minimum Inhibitory Concentration (MIC)

To assess the antimicrobial activities of the examined essential oil, the minimum inhibitory concentration (MIC) measurements, defined as the lowest concentration of the sample under investigation that inhibits bacterial or fungal growth after incubation at ideal temperature, were undertaken in 96 flat bottom microtiter plates (TPP, Switzerland) as formerly reported (**15**). Briefly, fresh overnight cultures of bacteria and yeasts were adjusted with media to an inoculum concentration of 1.0 x 10^5 CFU/per well. Positive controls, Ampicillin and Amphotericin B, and a negative control of untreated media were prepared under the same investigational conditions. Plates were incubated, with shaking, for 48h at incubation temperatures for the bacterial plates and the *Candida* plates of 37°C and 33°C, respectively. Optical densities were determined at wavelength 600 nm (OD_{600}) using a Microplate Reader (Palo Alto, CA, USA).

Determination of Antiproliferative Activity

Cells

All cell lines (MCF7, HeLa, PC3, and K562) were acquired from the American Type Culture Collection (Rockville, MD, USA). Cells were cultured in DMEM medium (Dulbecco's Modified Eagle's Medium), complemented with 10% Fetal Bovine Serum, 100 U/mL of Penicillin, 100 µg/mL of Streptomycin, at 37°C with 5% of CO_2. Viable cells count was resolved using the Trypan blue method as previously described (**16**).

MTT Assay

The antiproliferative activities of the examined essential oil was studied in 96-well round bottomed microplates employing the MTT assay (3-[4, 5-dimethylthiazole-2-yl]-2, 5-diphenyl- tetrazolium bromide) (Sigma-Aldrich, USA) as previously described (**16**). In summary, a cell seeding density of $1x10^4$ cells/mL was used for all cells in 96 well plates. Cells were incubated for 24 h to allow attachment. The examined essential oil was applied at different concentration onto each well in triplicates and incubated for 48 h. Afterward, 10 µL of 0.5 mg/mL of MTT solution was added to each well and further incubated for 4 hours before measuring the absorbance at 570 nm. Growth inhibition was determined according to the following equation:

%inhibition= 100-(mean of Abs of test sample-mean of Abs of negative control)x100/(mean of Abs of positive control-mean of Abs of negative control)%

For data analysis, the Graph Pad Prism 8 software was used to calculate the inhibition percentage and results were presented as LD_{50} value, regarded as the concentration that concedes 50% growth suppression. Doxorubicin was employed as a positive control under the same experimental conditions as for the test samples.

Data Analysis

All measurements were performed in triplicates, with the results expressed as mean ± SD of three independent experiments (n=9). The means were statistically compared using one-way ANOVA, applying a Student's t-test, with $\alpha = 0.05$. The analyses were carried out using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, New York, NY, USA).

Results and Discussion

Yield and Composition of Essential Oil

The essential oil yield of *Salvia officinalis* aerial parts was 0.84 % (v/w based on dry weight) and the density of the concentrated oil was 0.93 g/mL. The oil had light yellow color, was soluble in methanol with the characteristic strong fragrance of sage. Several studies have reported different yields of *S. officinalis* oil from various regions; Constantine region (Algeria) 0.65% (**17**), Tunis 0.58% (**18**), Libya 0.4% (**19**), and Bulgaria 0.93 % (**20**). The reported differences in essential oil of *S. officinalis* yield from the different geographical regions may be attributed to diverse factors such as harvesting season, temperature and extraction techniques (**21**).

The GC-MS analyses resulted in the identification of 39 major and minor compounds, representing 96.41% of the total oil composition. The percentages, Kovats indices and the retention time of the identified compound of this essential oil were summarized in Table 2. The principal components of the essential oil are camphor (16.41%), α-thujone (15.68%), manool (15%), viridiflorol (11.69%) and 1,8-cineole (10.06%). β-caryophyllene (5.05%), β -thujone (4.20%), α–humulene (3.03%) and camphene (2.71%) were also present at significant concentrations. Other components were present at amount lower than 2 % of the total oil. Studies on *S. officinalis* performed in Morocco (**22**), Tunisia (**23**) and Libya (**19**) revealed significant variations in the chemical composition of *S. officinalis* essential oil relative to the findings of the current study. For example, the chemical composition of *S. officinalis* essential oil cultivated in Tunisia was reported to contain great amounts of camphor (25.14 %), while α-thujone, 1,8-cineole, and viridiflorol were found at (18.83 %,14.14 %,7.98 %) respectively (**23**). Interestingly, *S. officinalis* essential oil reported in this study has different composition from that reported by other Algerian studies. Noteworthy, Dob *et al.* (**24**) reported the chemical composition of *S. officinalis* essential oil from Algiers city, located in the north of Algeria, to contain camphor (20.4%), α-thujone (19.6%), 1,8-cineole (12.3%), β-thujone (8.0%), and viridiflorol (8.0%) as the major components of the oil. The reported variation in chemical composition of the oil is likely attributed to the different growth habitat, environmental factors, genetic variations, the growth phase of the plants and the extraction method (**12, 24, 25, 26**).

Table 2: Chemical composition of *Salvia officinalis* essential oil

N°	Retention time (mn)	Components	Kovats indices	Percentages (%)
1	3,4	Z-Salvene	855	0.06
2	5,2	Tricyclene	923	0.06
3	5,4	α-Thujone	931	0.21
4	5,6	α-Pinene	938	1.20
5	6,2	Camphene	953	2.71
6	7,3	Sabinene	973	0.26
7	7,4	2-β- Pinene	980	1.76
8	8,3	β-Myrcene	994	1.60
9	8,9	1-Phellandrene	1006	0.09
10	9,6	α -Terpinene	1012	0.23
11	10,2	p-Cymene	1027	0.36
12	**10,6**	**1,8-cineole**	**1030**	**10.06**
13	12,3	γ -Terpinene	1059	0.50
14	12,9	Z-Sabinenehydrate	1073	0.21
15	14,2	α -Terpinolene	1084	0.88
16	**15,7**	**α-Thujone**	**1105**	**15.68**
17	16,3	β - Thujone	1115	4.20
18	**18,2**	**Camphor**	**1144**	**16.41**
19	19,0	Isopinocamphone	1161	0.09
20	19,4	Borneol L	1165	0.55
21	19,5	Isoborneol	1156	0.36

N°	Retention time (mn)	Components	Kovats indices	Percentages (%)
22	20,2	4-Terpineol	1174	0.32
23	21,2	α –Terpineol	1198	0.17
24	27,7	borneol acetate	1273	1.43
25	28,3	Sabinyl acetate	1287	0.16
26	36,0	β-Caryophyllene	1409	5.05
27	38,1	α -Humulene	1444	3.03
28	38,4	Allo-aromadendrene	1478	0.08
29	39,6	α -Amorphene	1470	0.15
30	39,7	(-)-Germacrene D	1480	0.09
31	40,6	α -selinene	1493	0.18
32	41,7	γ -Cadinene	1513	0.06
33	42,4	β-Cadinene	1524	0.21
34	45,6	(-)-Caryophyllene oxide	1581	0.86
35	**46,4**	**Viridiflorol**	**1590**	**11.69**
36	46,8	6,12-Epoxyspiroax-4-ene	1588	0.19
37	49,0	α-Cadinol	1653	0.15
38	49,4	β-Eudesmol	1654	0.11
39	**69,8**	**Manool**	**2055**	**15.00**
		Total (%)		96.41

Antioxidant DPPH Activity

Antioxidant activity of the *salvia officinalis* essential oil has been determined by one test system; the DPPH assay. The IC_{50} values (the concentration reducing 50 % of DPPH) obtained for scavenging activity on DPPH radical are presented in Table 3. In the DPPH assay, the ability of the investigated essential oils to act as donors of hydrogen atoms or electrons in transformation of DPPH into its reduced form DPPH-H was investigated. In this assay essential oil has demonstrated a reasonable activity to scavenging and decolorate the radical DPPH with an IC_{50}= 0.222 mg/mL relative to the standard ascorbic acid IC_{50} =0.075mg/ml. Our results come in great consistency with previous literature reports that correlate the efficiency of the antioxidant power of an essential oil to its content of monoterpenes hydrocarbons and oxygenated monoterpenes (**25, 26**). Noteworthy, it appears that the antioxidant activity of sage oil maybe due to its content of a known strong antioxidant, as α-pinene and several other sesquiterpenes (**27, 28**) with possible contribution from minor and major components to exhibit this activity.

Table 3. Antioxidant activity of the essential oils from *S. officinalis* and positive control (ascorbic acid) using the DPPH assay.

Sample	IC_{50} (mg/ mL)
Essential oil	0.222±0.013
Ascorbic acid	0.075±0.010

Antimicrobial Activity

The obtained MIC values of the investigated oil are presented in Table 4. As demonstrated by the results, *S. officinalis* essential oil possessed comparable bactericidal activity against the examined gram-positive bacteria (*Staphylococcus aureus* and *Staphylococcus epidermidis*) and gram-negative bacteria (*Escherichia coli*, and *Pseudomonas Aeruginosa*), with MIC values ranging between 136-212 µg/mL, suggesting a broad antibacterial spectrum. In contrast, very weak antifungal activity has been observed on the candida species under investigation. The literature is rich with reports that show potent antibacterial activity associated the essential oils from different species of sage. Our findings are consistent with

the previous literature reports indicating the wide spectrum of sage oil's antibacterial activity (**5, 6, 8**). Interestingly, the activity was attributed to certain chemical components of the oil, such as 1,8-cineole, camphor, α – and β-thujone, borneol, and p-cymene, among others (**6**). It has been suggested that these chemical components may exert their antimicrobial effects through the disruption of bacteria or fungal membrane integrity (**6; 9**). In addition, the sage oil studied here appears to contain fair quantities of oxygenated monoterpenes which may contribute to its antimicrobial activity (**8**). The pathogens studied in this report represent some human pathogens that are known to infect man and animal and may result in food deterioration and contamination Therefore, the reported antimicrobial activities are likely to be attributed to synergistic effects between the variable major and minor constituents of the oil, proposing that sage oil may potentially be beneficial in food preservation.

Antiproliferative activity

Salvia species have been extensively investigated for their chemical composition and pharmacological profile. Recently, there has been a growing interest in the field of essential oils (EOs) for the search of new naturally occurring anticancer molecules. Generally, EOs exert more potent anticancer activities than their individual components due to synergism (**29, 30, 31)**. Until today the anticancer activities of the Algerian *S. officinalis* EO had not been reported in human prostate and leukemia cell lines. Therefore, this investigation aimed to investigate the effects of the essential oil on human breast, cervix, prostate, and leukemia cancer cells. Results of the antiproliferative activity are summarized in Table 4. As can be seen, *S. officinalis* EO exhibited antiproliferative activity against all examined cancer cells, including the leukemia and prostate cancer cells, after only 48 hours of treatment with LD_{50} values of 214-363 µg/mL. Remarkably, the observed antiproliferative effects of the EO was possibly linked to its ability to infiltrate through the cell membrane. Morphological changes and modifications of the cell membrane were revealed after 48 hours of treatment using an inverted microscope.

Table 4. Antimicrobial (MIC) and antiproliferative (LD_{50}) activities of *S. officinalis* essential oil (mean ± SD).

Sample	Antimicrobial activity [a]						Antiproliferative activity[b]			
	S. epidermidis	***S. aureus***	***E. coli***	***P. aeruginosa***	***C. glabrata***	***C. albicans***	**MCF-7**	**HeLa**	**PC3**	**K562**
Oil	140±9	136±11	168±17	212±12	420±13	512±18	214±10	219±13	230±11	363±9
Control	2 [a]	2 [a]	16 [a]	128 [a]	2 [a]	2 [a]	1[b]	5[b]	25[b]	25[b]
Student´s t-test	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

(a) Antimicrobial activity of *S. officinalis* oil measured by MIC (µg/mL, mean ± SD). Results represent the means of three independent readings ±SD (n=9). Positive controls were Ampicillin (antibacterial) and Amphotericin B (antifungal) (**b**) Antiproliferative activity evaluation of *S. officinalis oil* by MTT assay in the examined human cancer cell lines, exposure time 48 h. The presented LD_{50} values are expressed as µg/mL ± SD and correspond to the means of three independent readings (n=9). Doxorubicin was the positive control anticancer agent. A Student´s *t*-test was used to determine the significant difference between two different samples, with $\alpha = 0.05$.

Considering these findings and the results reported elsewhere in the literature, further investigations should be encouraged to investigate the mechanism of action of alternative naturally occurring anticancer molecules from the Algerian *S. officinalis* EO.

Conclusion

Taken together, this study provides a full characterization of the chemical and biological profiles of the Algerian *S. officinalis* essential oil. The chemical composition of the oil revealed thirty-nine components

representing 96.41% of the essential oil with camphor (16.41%), α-thujone (15.68%), manool (15%), viridiflorol (11.69%) and 1,8-cineole (10.06%) as the major compounds. The oil appeared to have reasonable antioxidant properties compared to ascorbic acid in the DPPH assay. Broad spectrum antimicrobial activities were observed against the examined Gram-positive and Gram-negative bacteria. The oil exhibited growth inhibition properties against breast, cervical, leukemia and prostate cancer cell lines that could suggest a potential use for the oil as a nutraceutical for cancer prevention.

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التركيب الكيميائي والتقييم البيولوجي للزيت العطري لنبات *Salvia officinalis* L من الصحراء الجزائرية

محجوبي الحاج عيسى[1]، بقشيش بولنوار[1]، غريب عبد العزيز[1]، فضيلة بوجلال[2]، سناء برديول[2]

1 جامعة عمار الثليجي– الأغواط – الجزائر
2 كلية الصيدلة، الجامعة الأردنية، الاردن

ملخص

في هذه الدراسة، تمت دراسة التركيب الكيميائي والأنشطة البيولوجية للزيت العطري من نبات *Salvia officinalis* ، وهو نبات محلي يزرع في الأغواط (الصحراء الجزائرية). تم تحديد التركيب الكيميائي للزيت العطري بواسطة الفصل الكروماتوجرافي الغازي / قياس الطيف الكتلي (GC / MS). تم اكتشاف 39 مكونًا يمثلوا 96.41٪ من الزيت العطري باستخدام الكافور (16.41٪) ، ألفا ثوجون (15.68٪) ، مانول (15٪) ، (11.69) viridiflorol٪ و (cineole 10.06)٪–1.8 كمركبات رئيسية. تم استخدام النشاط المضاد للأكسدة عن طريق ازالة الجزيئات الحرة من خلال 2،2–ثنائي فينيل 1–بيكريل هيدرازيل (DPPH). كانت قيمة IC_{50} للزيت العطري 0.222 مجم / مل في اختبار DPPH والتي يمكن اعتبارها قوة معقولة من مضادات الأكسدة. تم تقييم الأنشطة المضادة للميكروبات على بكتيريا مختارة موجبة الجرام وسالبة الجرام، وكذلك على نوعين من الفطريات الممرضة. أظهرت النتائج نشاطًا مضادًا للبكتيريا مقبول وواسع النطاق بينما أظهر الزيت إمكانات ضعيفة كمضاد للفطريات. من ناحية أخرى، تم تقييم إمكانات الزيت كمانع للتكاثر على أنواع مختلفة من الخلايا السرطانية البشرية مع تسجيل نشاط للزيت على اللوكيميا وسرطان البروستات لأول مرة في الدراسات. كانت قيم LD_{50} للزيت ما بين 200–400 ميكروغرام / مل على أنواع السرطان المختلفة التي تم فحصها. هذه النتائج تشجع على إجراء مزيد من الأبحاث عن الاستخدام المحتمل لزيت الميرمية العطري كمكون بيولوجي طبيعي نشط في صناعة الأغذية والأدوية.

الكلمات المفتاحية: *Salvia officinalis* ، الزيوت العطرية ، التركيب الكيميائي ، مضادات الأكسدة ، مضادات التكاثر، مضادات الميكروبات.

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