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Comparing the Anticandidal Activities of *Salvia macrosiphon* essential oil and Fluconazole

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ABSTRACT

Aims Candidiasis is the most opportunistic infection with a high rate of recurrent infection. *Salvia macrosiphon* has an antibacterial effect; however, its antifungal effect was not studied. This study aimed to investigate the chemical composition of essential oil from leaves of *Salvia macrosiphon* and its antifungal activity compared with fluconazole.

Materials & Methods *Salvia macrosiphon* leaves, a native plant of Kogiluyeh and Boyerahmad province, were collected from Zagros Heights and used in this study. Then, the essential oil of this plant was tested for antibacterial and antifungal properties and compared with fluconazole. The chemical composition of the essential oil was analyzed by GC/MS (Gas Chromatography Mass Spectrometry), and the antifungal activity of the plant's essential oil was compared with that of fluconazole.

Findings The results of GC-MS analysis proved the presence of at least 29 compounds in the essential oil of *Salvia macrosiphon*. Amon these constitute butyl benzoate (49.16%), n-hexyl benzoate (7%), and isopatolenol (4.83%) were the main compounds. The minimum inhibitory concentration (MIC) of the essential oil (µl/ml) of *Salvia macrosiphon* and fluconazole (µg/ml) were 0.44 and 0.7 for Candida albicans, 0.056 and 0.7 for *C. glabrata,* and 0.1 and 0.088 for *C. parapsilosis*, respectively. Also, statistical analysis demonstrated a significant difference between the mean of fluconazole and essential oil in total Candida isolates (p=0.001).

Conclusion The essential oil of Salvia macrosiphon has stronger antifungal activity than fluconazole.

Keywords *Salvia macrosiphon*; Essential Oils; *Candida albicans*; *Candida glabrata; Candida parapsilosis*

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Introduction

Candidiasis is the most opportunistic infection and causes a variety of clinical forms. This infection may be superficial (e.g., oral, nail), mucocutaneous (e.g., vaginal), or systemic (e.g., candidemia, candiduria) [1]. Different species of *Candida* have been introduced as agents of candidiasis such as *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. krusei*, and *C. dubliniensis* [2]. Although *C. albicans* is the most common cause of the disease, the prevalence of non-albicans species is also increasing [3]. Even though common *C. albicans* infections are easily treatable, systemic infections, frequently nosocomial, have a high mortality rate.

Therefore, early diagnosis and management of infection are necessary [4]. There are different classes of antifungal drugs and uses for various forms of candidiasis. These drugs included azole classes (e.g., imidazole and triazole), echinocandin (e.g., caspofungin), and polyene (e.g., amphotericin B) [5]. Fluconazole is one of the triazole drugs and is widely used in mucocutaneous and systemic forms of candidiasis. In the past two decades, several genes and mutations that increase resistance to fluconazole in clinical isolates, primarily in C. albicans, have been elucidated [6].

The use of herbal plants and their products has been considered for a long time. Some properties, such as ease of access, lack of side effects, and drug resistance, have always caused these compounds to be used to treat various diseases. The genus of Saliva belongs to the Lamiaceae family and possesses more than 100 species. Many countries have been introduced as the inhabitants of this genus [7]. Iran is also an endemic region of this genus, with 61 flora species in it [8]. Generally, Saliva species are used in foods, cosmetics, perfumery, and pharmaceutical industries. *Salvia macrosiphon*) *S. macrosiphon*), known as Maryam Goli Lolei or Marvak in Persian, has been used in traditional medicine. This species is the most valuable type of the Lamiaceae family and has therapeutic effects. The habitant of this species is in Iran and Afghanistan, and due to its essential oil and tannin, its leaves have a strengthening and tonic effect; in addition, they facilitate digestion, are diuretic, anticonvulsant, antipyretic, and reduce blood sugar. It is used externally to heal and disinfect wounds [9]. Some fractions of *S. macrosiphon* have been introduced as antibacterial agents. For instance, the antibacterial effects of the plant's n-hexane, chloroform, and ethyl acetate fractions on Staphylococcus aureus and E. coli were tested in one study, and the results showed good activity with MIC values ranging from 0.61 to 2.5mg/mL [10]. Today, the problem of resistance of Candida species to existing chemical drugs, as well as complications and high cost of chemical drugs, is observed, and there is a tendency to use medicinal plants as medicinal and antifungal compounds [11].

Therefore, this study aimed to investigate the chemical composition of essential oil from leaves of *Salvia macrosiphon* and compare its antifungal activity with fluconazole.

Materials and Methods

Design and samples

This study was designed based on the clinical laboratory research method from 2021 to 2022. Fifty-six *C. albicans* isolates were collected from the patient's samples, including vulvovaginal swabs, ear swabs, and blood and urine specimens studied.

Plant material

The aerial parts of *S. macrosiphon* were collected. The identification process was done and approved in the Kerman Agriculture and Natural Resources Research and Education Center, and the herbarium number was obtained (herbarium number: 17714). The aerial parts were crushed and dried at room temperature. 200g of dried powder mixed with 1L of distilled water and the essential oil hydrodistilled in a Clevenger apparatus according to the British method for 3h. Finally, the essential oil was preserved at 4ºC in a dark condition until other steps.

Gas chromatography/Mass spectrometry

The GC/MS method was used to analyze the components of the essential oil of the *S. macrosiphon* fruit at Kashan University of Medical Sciences. Chromatography instrument Model 6890 (Agilent; United States) and mass spectrometry were used for qualitative and quantitative measurements of compounds. The temperature was set at 60°C, then raised to 246°C at a rate of 3°C. The combination of gas chromatography and mass spectrometry characteristics is used to identify different substances present in a sample.

Antifungal susceptibility test

Preparation of Candida isolate

56 *C. albicans* (including 15 blood cultures, 40 vulvovaginitis, recurrent vulvovaginitis, and 1 otomycosis isolates), 12 *C. glabrata* (6 vulvovaginitis, 6 urine culture isolates), 12 *C. parapsilosis* (3 blood cultures, 9 otomycosis isolates) were studied. Candidal isolates were collected from the patient's samples (vulvovaginal swabs, ear swabs, and blood and urine specimens).

Vaginal samples were taken from suspected patients with VVC that had been referred to gynecology and (obstetrics) private midwifery clinics in Yasuj, Iran, from 2021 to 2022. Other samples, including blood culture, urine, and ear swabs, were referred to the Yasuj University of Medical Science medical school and identified based on molecular methods. All *Candida* isolates were subculture on Sabouraud Dextrose Agar (Biolife; India) and incubated at 37°C. Then fresh isolates were used for other steps.

Determination of minimum inhibitory concentration (MIC)

An antifungal susceptibility test was carried out based on CLSI-M27-A3 guidelines [12]. Fungal suspensions were prepared by fresh colonies and distilled water and standardized using a Model 6320D Spectrophotometer (JENWAY; China) in 530nm and 75-77 transmittance. For broth microdilution processes, essential oil and fluconazole were diluted in RPMI 1640, and 100µL of each diluted solution was added to the 96-well microtiter plate. The standard fungal suspensions were also diluted 1:1000 in RPMI 1640 medium and added to each well. All microplates were incubated at 37°C for 24-48h. Growth inhibition was determined after the incubation period and compared with positive control.

Statistical analysis

Data were entered into Excel 2016 and analyzed in SPSS 16 software using descriptive statistics, and the Wilcoxon test was calculated. Also, the data distribution was checked using the Shapiro-Wilk and Kolmogorov-Smirnov tests, and it was not normal in any of the groups. Due to non-normality, non-parametric tests were used for data analysis.

Findings

Overall, 29 components were identified in the leaf essential oil (Table 1). The main constituents of the oil were Butyl benzoate (49.16%), n-hexyl benzoate (7%), Isospathulenol (4.8%), Cyperene (4.1%), Benzoic acid, 2-methyl-, butyl ester (3.88%), beta-caryophyllene (3.54%), and β-Elemene (3.02%).

Table 1. Chemical component of *Saliva macrosiphon*

PK	Name	RT (min)	Standard Retention Index	Conc.
1	Methyl benzoate	17.707	1091	0.27
2	linalool	17.844	1098	3.31
3	Hexyl isobutyrate	19.461	1150	0.82
4	Ethyl benzoate	20.496	1170	0.31
5	Hexyl 2-methylbutanoate	22.690	1234	0.65
6	Hexyl 3-methylbutanoate	22.896	1243	0.34
7	Propyl Benzoate	24.09	1247	0.77
8	Butyl benzoate	26.416	1339	49.16
9	Octyl isobutyrate	27.669	1348	0.98
10	β-Elemene	28.286	1375	3.02
11	Cyperene	29.240	1398	4.10
12	Benzoic acid, 2-methyl-, butyl ester	29.440	1409	3.88
13	beta-caryophyllene	29.777	1418	3.54
14	(+)-Aromadendrene	30.555	1439	0.39
15	alpha-Humulene	31.166	1443	1.34
16	(E)-germacrene D	31.338	1480	1.62
17	Bicyclogermacrene	31.441	1494	0.71
18	δ-Selinene	31.784	1495	2.86
19	n-Hexyl benzoate	32.955	1576	7
20	Caryophyllene oxide	34.321	1581	1.19
21	Salvial-4(14)-en-1-one	34.504	1589	0.77
22	Ledene	35.556	1600	0.41
23	Caryophyllenol II	35.721	1614	0.93
24	Isospathulenol	36.379	1623	4.83
25	Isoaromadendrene epoxide	37.024	1682	2.29
26	Heptadecane	39.191	1700	0.45
27	Benzyl benzoate	39.545	1762	0.68
28	Octyl benzoate	39.905	1766	2.75
29	Palmitic acid	44.186	1984	0.63

Table 2. Minimum inhibitory concentration range, MIC_{50}, MIC_{90}, and $MIC_{GeoMean}$ (MIC_{GM}) of *S. macrosiphon* compared with fluconazole against *Candida* species

Organisms	*S. macrosiphon* (µl/ml)				Fluconazole (µg/ml)			
	MIC range	MIC_{50}	MIC_{90}	MIC_{GM}	MIC_{range}	MIC_{50}	MIC_{90}	MIC_{GM}
***Candida albicans* (n=56)**	0.039-2.5	0.078	0.46	0.44	0.0625-4	1	2	0.7
***Candida parapsilosis* (n=12)**	0.039-0.15	0.078	0.141	0.1	0.0312-0.5	0.18	0.5	0.088
***Candida glabrata* (n=12)**	0.039-0.15	0.078	0.078	0.056	0.0625-32	0.5	7.6	0.7

Antifungal activities

According to the MIC value *S. microsiphon* had a better effect against different Candida species. Besides, the MIC value range was lower in non-albicans species (0.039-0.15µl/ml) than *C. albicans* (0.039-2.5µl/ml). Based on MIC_{90}, fluconazole had poor activity against *C. glabrata* isolates (7.6µg/ml). However, a comparison of MICGM between *S. macrosiphon* and fluconazole revealed that only *C. parapsilosis* had this value lower in fluconazole (0.088µg/ml). Statistical analysis showed a significant difference between the mean of fluconazole and essential oil in total *Candida* isolates (p=0.001; Table 2).

Table 3. Comparison of the mean of different Candida species in two essential oil and fluconazole groups (Wilcoxon test)

Microorganism	*S. macrosiphon*	Fluconazole	p-Value
C. albicans	0.281±0.583	1.489±4.234	0.0001
C. parapsilosis	0.0867±0.0315	0.242±0.168	0.003
C. glabrata	0.677±0.0323	4.234±9.077	0.002

A mean and standard deviation comparison showed that Candida isolates in *S. macrosiphon* essential oil were lower than fluconazole (Table 3).

The difference in antifungal activity between *S. macrosiphon* essential oil and fluconazole was significant in all Candida species ($p<0.05$).

Discussion

Candidiasis is the most opportunistic infection, and its treatment has always been challenging [13]. The drug resistance of Candida isolates which are sometimes intrinsic and mostly acquired, has made it difficult to treat patients [14]. Therefore, choosing a suitable drug with the lowest cost and no recurrence of infection has always been desired. Herbal medicines with low side effects and availability have long been interesting [15]. In this study, the essential oil of *S. macrosiphon* was analyzed using the GC-MS method, and its constituent elements were determined. The most compounds in this essential oil

are butyl benzoate (49.16%), n-hexyl benzoate (7%), isopatolenol (4.83%), cuprene (4.10%), benzoic acid 2-methyl-1-butyl ester (3.88%), linalool (3.31%), beta-caryophyllene (3.54%), and beta-Elemene (3.02%). Various studies investigated the main compounds found in different species of Saliva. For example, in the study, Sajadi *et al.* proved the presence of at least forty-six compounds in the essential oil of *S. macrosiphon*. Among these compounds, beta-pinene (15.3%), germacrene-di (10.1%), spatholenol (7.7%), and 1 and 8-cineole (7.4%) were the main compounds in the essential oil of *S. macrosiphon* [16]. Also, in the study conducted by Taari *et al.*, the most important components of the essential oil of this plant, 9- and 8-cineole, alpha-thujone, viridiflurol, and beta-thujone, were introduced [17]. This is even though the above compounds were not detected in the present study. The difference in the composition of Salvia species essential oil can be attributed to ecological differences. The compounds in the essential oils of plants are caused by ecological differences such as latitude and longitude, altitude, temperature, humidity, climate and soil, metabolic pathways, and biosynthesis of effective substances in these plants, which result in various secondary metabolites being biosynthesized under different environmental conditions. Various studies have confirmed this. Also, in similar weather conditions, secondary compounds in different plants have similarities. Of course, the conditions and types of studies are different, which can affect the results.

The present study was done to test the antifungal activity of *S. macrosiphon* based on the microdilution method. In the literature, the antimicrobial activity of some genera of Salvia essential oils against microbes has been reported [9, 18]. However, the use of the broth microdilution method in the effect of antifungal activity of *S. macrosiphon* has been done for the first time in Iran in the present study. The results of the present study showed that the essential oil of *S. macrosiphon* had great activity against Candida isolates. So, the essential oil of *S. macrosiphon* affected the growth of *C. albicans*, and the MIC_{50} of this plant was equal to 0.78µl/ml. the MIC_{50} value was 1µg/ml for fluconazole against *C. albicans* isolates. Agreeing with the present study's results, the study conducted by Atai *et al.* reported MIC=1µg for Saliva species against *C. albicans* [19]. Also, in the study of Banaeian-Boroujeni *et al.*, *S. officinalis* with a concentration of 1.25µg/ml was able to inhibit the standard strain of C. albicans [20]. However, in the study of Sookto et al., the effect of the extract and oil of several plants from the Lamiaceae family, including *S. officinalis* and Chamomile, on *C. albicans* was investigated. S. officinalis essential oil, with a concentration of 78.2mg/l, inhibited the growth of *C. albicans* [21]. Pozzatti *et al.* reported that the essential oil of *S. officinalis* had no effect against fluconazole resistance and susceptible *C. albicans* [22]. This difference between our results and Pozzatti *et al.*, may be due to the different species of Salvia tested. Besides, the present study revealed that *S. officinalis* essential oil had an inhibition effect against *C. glabrata* isolates (MIC_{GM}=0.056µL/ml). This antifungal activity has a better inhibitory effect than fluconazole (MIC_{GM}=0.7µg/ml) against *C. glabrata* isolates. However, Salari *et al.*, reported the methanolic extract of *S. rhytidea* had anti-fungal activity against *C. glabrata* isolates (MIC50=100µg/ml) [23]. Resistance to fluconazole has been reported during treating different forms of candidiasis [24, 25]. There is no study similar to the present study for the effect of *S. macrosiphon* on Candida isolates and its comparison with fluconazole. However, the results of the present study indicated that the MIC_{50} value of *S. macrosiphon* was lower than that of fluconazole against Candida isolates.

The mechanism of the inhibitory effect of *S. macrosiphon* is not clear. In one study, it was mentioned that it was probably due to the destruction of the cell wall by lipophilic compounds in this mechanism. Significant leakage of cell material indicates irreversible cell membrane damage [26]. On the other hand, the difference in the concentration of Saliva species in inhibiting the growth of Candida, which is observed in the results of various research, can be due to geophysical factors and different species of this plant or the methods of essential oil extraction, oil preparation, and laboratory methods [23, 27, 28].

One limitation of this study is the limited effect of essential oil on clinical isolates in vitro examination and the lack of simultaneous comparison in vivo conditions. Based on the results of this study, it can be hoped that recurrent candidal infections will be treated in the future with different formulations of *S. macrosiphon* along with antifungal drugs. However, confirmation of the present results in similar studies is necessary. Therefore, in future studies, this issue can also be investigated in the patient with candidiasis.

Conclusion

Saliva microsiphon has greater anticandidal activity than fluconazole. Therefore, it is hoped that it will be used as an antifungal compound in treating Candida infections in the future.

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Salahi M (Sixth Author), Introduction Writer (10%); Gharaghani M (Seventh Author), Assistant Researcher/Discussion Writer (25%)

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