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Anticandidal effects and chemical compositions of volatile oils extracted from *Origanum syriacum*, *Clinopodium serpyllifolium* subsp. *fruticosum* and *Thymbra capitata* from Palestine

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Abstract

Background Over the past decade, researchers have been exploring the potential therapeutic benefits of volatile oils (VOs) in addressing various disorders, particularly those associated with an increase in fungal infections. This study aimed to analyze the chemical compositions of three different thyme species growing in Palestine using gas chromatography–mass spectroscopy (GC–MS) and explore their antifungal characteristics. The thyme species investigated in this research encompass *Origanum syriacum* L., *Clinopodium serpyllifolium* subsp. *fruticosum* (L.) Bräuchler, and *Thymbra capitata* (L.) Cav.

Methods The VOs of the investigated plants were extracted by hydrodistillation technique equipped with Cleavenger apparatus and characterized by utilizing GC–MS equipment. Moreover, the extracted VOs were evaluated for their antifungal activity using the broth microdilution assay against several clinically isolated Candida species and one ATCC strain.

Results The GC–MS characterization results of *O. syriacum* VO revealed the presence of 22 components and the abundant molecules were thymol (37.36%), carvacrol (27.71%), γ-terpinene (17.47%), and p-cymene (7.80%), while 19 compounds were characterized in the *C. serpyllifolium* VO and the major components were *p*-cymene (37.58%), carvacrol (22.93%), and γ-terpinene (21.91%). In addition, 23 compounds were identified in *T. capitata* VO and the main components were carvone (59.45%), pulegone (21.59%), menthone (4.24%), and isomenthone (3.71%). According to the antifungal assay results, VO extracted from *O. syriacum* has the highest activity among all the screened VOs.

Conclusion All the VOs screened in this study exhibit promising antifungal activities for various potential medical applications. Consequently, we strongly advocate for further biological investigations of these oils in the near future.

Keywords *Origanum syriacum*, *Clinopodium serpyllifolium* subsp. *fruticosum*, *Thymbra capitata*, Volatile oils, Anti-Candida

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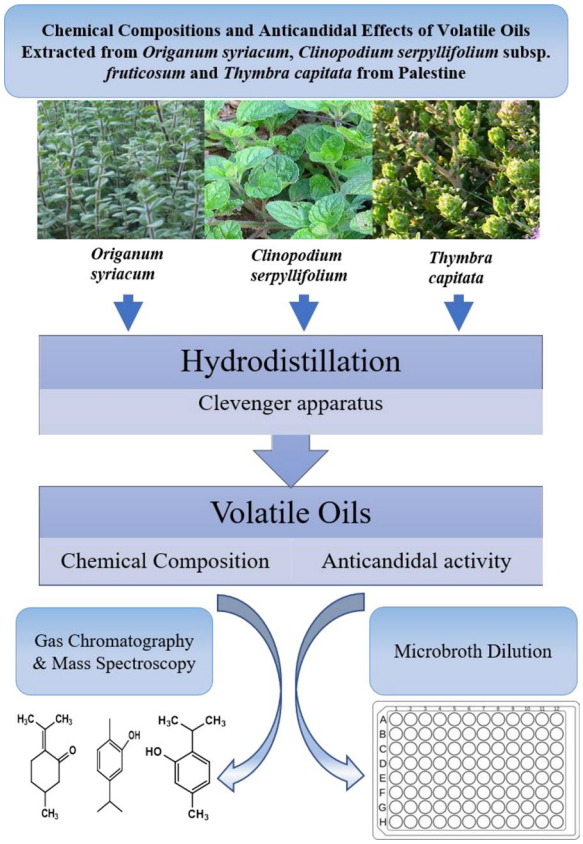
Graphical Abstract



Introduction

In recent years, there has been a noticeable increase in interest in investigating the medicinal potential of plants, with the majority of these studies focusing on historically utilized plants for food and medicine [1–3]. These natural remedies offer several advantages, including fewer side effects, cost-effectiveness, and non-toxic properties than synthetic drugs [4]. A contemporary treatment method has emerged that combines herbal supplements with traditional chemotherapeutic drugs to increase efficacy while minimizing side effects [5]. However, herbal medicine is not subjected to the same regulatory processes as conventional medicine [6–8].

This investigation seeks to evaluate the therapeutic potential of chemicals found in the VOs of three Palestinian thyme species: *Origanum syriacum* L. *syriacum* is a perennial aromatic herb that is native to western Asia, southern Europe, and the eastern Mediterranean [9]. It can be found growing in the open or under cultivation. The leaves, which are commonly used as Arab seasonings, have been incorporated into baked goods, teas, fragrances, and flavors, as well as traditional, complementary, and alternative medicine [10]. *Clinopodium serpyllifolium* subsp. *fruticosum* (L.) Bräuchler is a profusely aromatic perennial herbaceous plant in Palestine's flora. This plant's leaves and flowers are loaded with potent phytochemicals that have been used to treat a variety of medical conditions for centuries [11]. Its medicinal characteristics, such as its antimicrobial potential, have been the subject of several investigations [12].

Thymbra capitata (L.) Cav. is an aromatic medicinal and culinary herb that grows in a variety of Mediterranean regions and possesses significant therapeutic properties that are primarily attributable to its VO constituents [13]. The VO of *T. capitata* is highly valued and economically significant due to its unique biological properties. Previous investigations revealed many potential effects, one of which is antimicrobial activity [14].

Candida is a yeast genus that is one of the most common causes of fungal infections worldwide [15]. *Candida* species are found as endosymbionts in a variety of human body locations, including the urogenital tract, the

gastrointestinal tract, and the skin [16]. While women are more susceptible to vaginal yeast infections, men can also be affected. Certain factors, such as long-term antibiotic use, put both men and women at risk. Fungal infections are more common in diabetics and people who are immunocompromised [17, 18]. A number of *Candida* species are well known in medicine for causing diverse illnesses, with *C. albicans, C. parapsilosis*, *C. tropicalis*, and *C. glabrata* causing the majority of opportunistic infections. These are either superficial or systemic infections of adults and neonates involving the bloodstream, urinary tract, vagina, esophagus, and oral cavity [19–22].

Numerous studies have explored the antifungal properties of VOs, focusing on their potential to hinder the growth of fungal pathogens [23–25]. While significant headway has been made in understanding these effects, a noticeable research gap pertains to the distinct chemotypes of VOs from different plant sources and their effectiveness against fungal infections. Moreover, a fresh approach to combat *Candida* infections has emerged: targeting essential functions crucial for the pathogen's virulence [26].

In this study, we looked at the chemical compositions and antifungal activities of VOs obtained from three flourish thyme species (Lamiaceae family): *O. syriacum* (local name: زعتر عادي), *C. serpyllifolium* subsp. *fruticosum* (local name: زعتر فارسي) and *T. capitata*. (local name: زعتر بلاط).

Material and methods

Plant samples collection, preparation, and extraction of VOs

During the flowering time, *O. syriacum*, *C. serpyllifolium*, and *T. capitata* leaves were gathered from the northern regions of Palestine in May 2021. The plants' samples were recognized by the pharmacognosist, Dr. Nidal Jaradat. A voucher specimen was deposited at the An-Najah National University in the Herbal Products Laboratory and deposed with the codes Pharm-PCT-A1729, Pharm-PCT-1575, and Pharm-PCT-690, respectively) at the same laboratory.

The herbs fresh leaves were dried in the shade at room temperature and relative humidity (25 ± 2 C, 55 ± 3 RH), respectively. The dried parts were pulverized to a fine powder of 60 µm in diameter and stored in airtight containers with adequate labeling for future use. All chemicals and reagents were of analytical grade and were supplied from Sigma-Aldrich (Germany). The VOs were extracted by the hydrodistillation technique [27]. Briefly, 100 mg of the dried leaves powder was suspended with 1 L of distilled water, and the VOs were extracted utilizing hydrodistillation with Clevenger apparatus operating at atmospheric pressure for 110 min at 100 °C. The obtained oils were chemically dried utilizing magnesium sulfate and stored at 2 °C until further use.

Gas chromatography/mass spectrometry (GC–MS)

Perkin Elmer Clarus 500 Gas Chromatograph apparatus was utilized for the characterizations of the *O. syriacum*, *C. serpyllifolium*, and *T. capitata* VOs components. This apparatus was connected to the Perkin Elmer Clarus 560 mass spectrometer. The separation was achieved by Perkin Elmer Elite-5-MS fused silica capillary column (film thickness 0.25 µm, 30 m × 0.25 mm). The components were recognized by associating the mass spectra of the components with authentic samples and/or the data from NIST, by interpreting the mass spectral fragmentation pattern of the molecules, and by relating retention indices (RIs) computed relative to a reference mixture of *n*-alkanes (C_6–C_{30}) [28].

Antifungal activity

Broth microdilution assay was used in the current study to estimate the antifungal activity of *O. syriacum*, *C. serpyllifolium*, and *T. capitata* VOs against clinically isolated Candida isolates and reference ATCC (90028) *Candida albicans.*

The VOs were dissolved in DMSO to a concentration of 100 µg/mL. The solution was serially micro-diluted (twofold) 10 times in sterile Brain Heart Infusion (BHI) broth. The dilution process was performed under aseptic conditions in 96-well plates. Wells number eleven contained plant-free BHI broth, which was used as a positive control for microbial growth. Wells number 12 contained plant-free and microbial-free BHI broth, which was used as a negative control for microbial growth. Wells 1–11 were inoculated aseptically with the test microbes. All the inoculated plates were incubated at 35 °C for approximately 48 h. The lowest VOs concentration with no visible microbial growth was considered to be the minimal inhibitory concentration (MIC). Fluconazole was used as a positive control for the antifungal activity [29, 30]. The VOs' antimicrobial activity was assessed in triplicate.

Results and discussion

Phytochemical GC–MS analysis

GC–MS analysis of *O. syriacum* VO revealed the presence of 22 components, accounting for 100% of the total VO. Approximately 97.05% are oxygenated monoterpenes and monoterpene hydrocarbons. Among the abundant identified compounds, were thymol (37.36%), carvacrol (27.71%), γ-terpinene (17.47%), and *p*-cymene (7.80%) (Table 1). The VO of *C. serpyllifolium* was also examined, and the GC–MS analysis revealed the presence of 19 distinct compounds. Monoterpene

Table 1 Chemical composition of *Origanum syriacum* volatile oil by GC/MS

Compounds names	RT	RI	Area	Area (%)
α-Thujene	8.43	926	22316344	0.55
α-Pinene	8.715	933	15056907	0.37
Camphene	9.371	949	965484	0.024
Sabinene	10.326	972	90,171	0.002
β-Pinene	10.531	977	2225893	0.06
Myrcene	11.096	991	56041152	1.38
Pseudolimonene	11.72	1006	8766395	0.22
α-Terpinene	12.187	1017	93908312	2.32
p-Cymene	12.522	1026	315772960	7.80
Limonene	12.702	1030	13145205	0.32
γ-Terpinene	13.937	1060	707024192	17.47
p-Mentha-3,8-diene	14.413	1071	7688733	0.19
Terpinolene	14.998	1086	2203380	0.05
Terpinen-4-ol	18.729	1182	5903295	0.15
Geranial	22.016	1272	42614388	1.05
Thymol	22.911	1297	1511935360	37.36
Carvacrol	23.186	1305	1121376896	27.71
Caryophyllene	27.023	1421	101738048	2.51
Cyclohexane, 1,5-diethenyl-3-methyl-2-methylene-, (1.alpha.,3.alpha.,5.alpha.)-	27.633	1441	3583605	0.09
α-Caryophyllene	28.163	1458	10160958	0.25
γ-Selinene	29.294	1493	2148218	0.05
Caryophyllene oxide	32.02	1585	2046809	0.05
Total			4046712705	100
Phytochemical classifications				
Monoterpene hydrocarbons				30.55
Oxygenated monoterpene				66.50
Sesquiterpene hydrocarbons				2.81
Oxygenated sesquiterpenes				0.05
Others				0.09

Table 2 Chemical composition of *Clinopodium serpyllifolium* subsp. *fruticosum* volatile oil by GC/MS

Compounds names	RT	RI	Area	Area (%)
α-Thujene	8.415	926	30072318	0.52
α-Pinene	8.69	933	109261160	1.88
Camphene	9.351	949	26881826	0.46
β-Pinene	10.501	977	22496034	0.39
Myrcene	11.076	990	59748988	1.03
α-Phellandrene	11.722	1006	9052438	0.16
α-Terpinene	12.182	1017	220667488	3.80
p-Cymene	12.557	1027	2183958016	37.58
Sylvestrene	12.697	1030	67563736	1.16
γ-Terpinene	13.927	1060	1273584512	21.91
Linalool	15.623	1101	47690072	0.82
Thymol, methyl ether	20.855	1237	17064442	0.29
Thymol	22.26	1279	71913096	1.24
Carvacrol	23.181	1305	1332486400	22.93
β-Caryophyllene	27.043	1421	263864176	4.54
Aromadendrene	27.633	1441	17536348	0.30
α-Caryophyllene	28.173	1458	11711415	0.20
Tricyclo[3.1.0.0(2,4)]hexane, 3,6-diethyl-3,6-dimethyl-, trans-	29.304	1494	10014292	0.17
Caryophyllene oxide	32.055	1586	36343880	0.63
Total			5811910637	100
Phytochemical classifications				
Monoterpene hydrocarbons				69.70
Oxygenated monoterpene				24.46
Sesquiterpene hydrocarbons				5.04
Oxygenated sesquiterpenes				0.63
Others				0.17

hydrocarbons (69.70%) and oxygenated monoterpenes (24.46%) constituted the largest groupings in VO. The most prevalent components were *p*-cymene (37.58%), carvacrol (22.93%), and γ-terpinene (21.91%) as shown in Table 2. Regarding *T. capitata*'s VO, it consisted of 23 distinct compounds, accounting for 99.82% of the total VO. Oxygenated monoterpenes (94.53%) were the predominant phytochemical class of the oil, which was composed of carvone (59.45%), pulegone (21.59%), methone (4.24%) and isomenthone (3.71%) as the principal constituents (Table 3).

Comparing our findings to those of Al Hafi et al.2016 [31], the main components of the VO of *O. syriacum* from Lebanon differ from Palestinian *O. syriacum* VO. In detail, the Lebanese *O. syriacum* VO mainly contains carvacrol (79%), whereas the carvacrol consists 27.71% from the Palestinian O. *syriacum* VO while thymol is the major component with 37.36%. Interestingly, thymol's anticandidal effect has been reported in other studies [24, 32, 33]. This variation in the chemical composition of the compositions of VOs from different populations of *O. syriacum* highlights the influence of environmental factors such as location and climate on the plant's secondary metabolites. Different dominating components, like carvacrol and thymol, may be responsible for variations in the VO's potential bioactivity and medicinal effects. The monoterpenes category constitutes the predominant compounds in VOs known for their anticandidal properties. Notably, these include *p*-cymene (found in 40 plants), linalool (in 35 plants), γ-terpinene (in 33 plants), carvacrol (in 31 plants), 1-8-cineole (in 30 plants), α-pinene (in 28 plants), and thymol (in 27 plants). Additionally, the sesquiterpene β-caryophyllene is present in 15 out of 100 plants, which could contribute to the expected antifungal activity based on the resulting chemical composition of various plants [26].

Table 3 Chemical composition of *Thymbra capitata* volatile oil by GC/MS

Compounds names	RT	RI	Area	Area (%)
α-Pinene	8.695	933	916462	0.04
Sabinene	10.316	972	1208114	0.05
γ -Pinene	10.506	977	7255872	0.29
Myrcene	11.046	990	1725107	0.07
Sylvestrene	12.67	1029	37489244	1.48
trans-Ocimene	12.79	1032	771712	0.03
p-Mentha-3,8-diene	14.403	1072	3101766	0.12
Isomenthone	17.569	1152	94158032	3.71
Menthone	18.094	1166	1076794	4.24
Isogeranial	18.494	1176	21165640	0.83
Trans-carveol	20.07	1218	52490524	2.07
Pulegone	20.585	1232	54859885	21.59
Carvone	20.885	1241	15105710	59.45
Verbinone	24.061	1332	5490790	0.22
1-Methylene-A21-hydroxymethyl-3,3-dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane	24.172	1335	3901987	0.15
Piperitenone	24.342	1340	28601542	1.13
Nepetalactone, cis, trans	24.622	1348	3219853	0.13
ND	24.812	1354	4483030	0.18
Piperitenone oxide	25.097	1363	25682604	1.01
Isoledene	25.562	1376	1733067	0.07
γ-Bourbonene	25.847	1385	997331	0.04
Trans-jasmone	26.157	1394	2639875	0.10
γ -Caryophyllene	27.003	1420	25682604	1.01
Caryophyllene oxide	32.03	1581	51474432	2.03
Total			2541038	99.82
Phytochemical classifications				
Monoterpene hydrocarbons				94.53
Oxygenated monoterpene				2.08
Sesquiterpene hydrocarbons				1.12
Oxygenated sesquiterpenes				2.03
Others				0.10

Regarding the Palestinian *T. capitata,* in comparison with those collected from Sicily and Spain reported by Verdeguer et al. [14], it was found that the carvacrol is the major component of *T. capitata* VO from Sicili (77.02%) and from Spain (77.13%), whereas carvone (59.45%) was identified as major components of the *T. capitata* VO growing in Palestine. These findings highlight the consistent presence of carvacrol in *T. capitata* VO and emphasize its significance in anticandidal effect that is also reported by Manohar et al. [25].

Antifungal activity

Due to their toxic nature and increasing resistance to current antifungal drugs, the treatment of Candida infections has become challenging. As a result, there is a pressing need for new antifungal agents and alternative approaches, particularly those derived from natural sources [34].

In recent years, the prevalence of fungal infections has risen, particularly among immunocompromised individuals such as those with HIV infection, those undergoing chemotherapy, and organ or bone marrow transplant recipients. These individuals are susceptible to various forms of fungal infections. *Candida* infections are extremely common in these individuals, resulting in oral, vaginal, and/or systemic candidiasis [35]. Furthermore, Abdalrazeq et al. [36] conducted a study on the *Thymbra* plant from Palestine, comparing it with the Turkish *Thymbra* previously analyzed by Baydar et al. [37], the

VOs derived from Turkish *Thymbra* exhibited microbial growth inhibition at concentrations below 1/100 (*v*/*v*), whereas the Palestinian *Thymbra* demonstrated antimicrobial effects at concentrations below 1/800. This observation suggests that the Palestinian *Thymbra* extract exerts stronger antimicrobial activity than its Turkish counterpart, likely attributed to regional differences between the two plants.

In the present study, the antifungal activity of the screened VOs against *Candida* species was evaluated using the microbroth dilution assay. The results showed that all the tested VOs exhibited antifungal effects. Notably, the VOs extracted from *O. syriacum* and *C. serpyllifolium* have the highest anticandidal activity against the *C. albicans* ATCC strain. While the *T. capitata* MIC value was very close to fluconazole. Interestingly, the VO extracted from *O. syriacum* revealed the highest potential against the clinical strains of *C. parapsilosis, C. tropicalis,* and *C. albicans* which is also of higher potential than fluconazole. Moreover, *C. serpyllifolium* VO showed strong inhibitory effects almost on the growth of all clinical strains. Finally, all tested VOs displayed strong antifungal activity compared to fluconazole, which was used as a positive control for the antifungal assay Table 4.

The observed potent anticandidal effects of the VOs extracted from *O. syriacum*, *C. serpyllifolium*, and *T. capitata* can be attributed to the unique chemical compositions of these plant VOs. In *O. syriacum* VO, the dominant presence of thymol, carvacrol, γ-terpinene, and p-cymene plays a pivotal role. Thymol and carvacrol, renowned for their antimicrobial properties, likely contribute significantly to the robust antifungal activity. These phenolic compounds are known to disrupt cell membranes and vital cellular processes, leading to Candida species' growth inhibition [38]. Similarly, *C. serpyllifolium* VO's effectiveness can be linked to its abundant p-cymene, carvacrol, and γ-terpinene content, all acknowledged for their anticandidal potential [39, 40]. These compounds may collaborate synergistically to exert strong inhibitory effects. In *T. capitata*, the high proportion of oxygenated monoterpenes, particularly carvone and pulegone, underpins the VO's potency. Carvone exhibits antifungal properties through membrane disruption, while pulegone may contribute to this effect and potentially target specific pathways in Candida species [41]. The minor compounds in these VOs might also contribute synergistically or independently to the observed activity. Overall, the distinctive chemical profiles of these plant VOs, rich in well-known antimicrobial components, likely underlie their potent anticandidal effects. Further mechanistic studies could shed light on the exact interactions and pathways that contribute to the observed activities.

In summary, the VO extracted from *O. syriacum* has the highest anticandidal activity among all the screened VOs. However, it is worth noting that previous studies (Table 5) have also reported promising anticandidal activity of *T. capitata*, *C. serpyllifolium*, and *O. syriacum* VOs against clinical strains of *C. glabrata*, *C. albicans, C. tropicalis,* and *C. parapsilosis.*

Considering the intricate chemical composition of plants' oils and the tendency for biological effects to stem from synergistic interactions among their diverse components, pinpointing the primary active compounds is challenging. The assessment of MIC values on reference strains of *C. albicans* suggests that certain monoterpenes and their derivatives play a crucial role in plants' oils exhibiting potent antifungal properties. Notably, compounds such as terpinyl acetate, α-terpineol, β-linalool, and γ-terpinene demonstrate robust anti-Candida activity when they constitute major constituents within the oils as in the case of Salvia mirzayanii, Plectranthus caninus Roth, and Thymus willdenowii Boiss [44, 45]. Conversely, the compounds comprising a significant portion of the plants' oil may not always be directly accountable for their activity. This further complicates the challenge of establishing a direct correlation between the plants' chemical composition and its biological effectiveness.

Extensive research has been dedicated to exploring the antifungal potential of individual acyclic and cyclic

Table 4 Antifungal microbroth dilution assay MIC (µg/mL) values of *T. capitata*, *C. serpyllifolium* and *O. syriacum* VOs

Source of *Candida* species	**Fungus**						
	ATCC	**Clinical strains**					
Assigned name/number	**ATCC 90028**	**151**	**168**	**202**	**205**	**209**	**260**
Microbes	*C. albicans*	*C. parapsilosis*	*C. tropicalis*	*C. albicans*	*C. glabrata*	*C. albicans*	*C. tropicalis*
T. capitata	1.56	12.5	12.5	6.25	6.25	12.5	12.5
C. serpyllifolium	0.39	0.39	0.39	0.39	0.195	0.195	0.39
O. syriacum	0.39	0.195	0.195	0.195	0.195	0.195	0.39
Fluconazole	1.95	0.24	1	0.24	32	0.5	1

Table 5 Previous investigations examined the antifungal activity of *T. capitata, C. serpyllifolium*, and *O. syriacum* VOs against *C. glabrata, C. albicans, C. tropicalis*, and *C. parapsilosis* using a microbroth dilution test (MIC values)

Plants	Candida strains	MIC values	References
Clinopodium serpyllifolium	*C. albicans* (clinical strain)	0.206 µg/mL	[42]
Origanum syriacum	*C. tropicalis* (clinical strain)	1.25 µL/mL	[26]
	C. albicans (clinical strain)	400 to 1200 µg/mL	[31]
Thymus capitatus	*C. albicans* ATCC	0.16–128 µL/mL	[43]
	C. parapsilosis (clinical strain)	0.32 µL/mL	
	C. tropicalis (clinical strain)	0.32 µL/mL	
	C. albicans (clinical strain)	0.16–128 µL/mL	
	C. glabrata (clinical strain)	0.32 µL/mL	
	C. albicans (clinical strain)	0.16–128 µL/mL	
	Candida tropicalis (clinical strain)	0.32 µL/mL	

monoterpenes [46, 47]. Among the tested compounds, α-terpineol, terpinen-4-ol, 1,8-cineol, and β-linalool have been documented to exhibit particularly swift fungicidal activity. In contrast, γ-terpinene, α-terpinene, terpinolene, and p-cymene displayed a somewhat slower yet still substantial antifungal effect. This dichotomy implies that the presence of the alcohol functional group holds greater significance than the specific cyclic or acyclic structure, concerning the rapid inhibitory impact on fungal growth. This phenomenon is attributed to the superior water solubility of alcohols within aqueous environments and microbial membranes [48, 49]. The recognition of plant species exhibiting notable anti-Candida activity could serve as a foundational step for a taxonomic strategy aimed at screening closely related species. This approach holds promise in uncovering valuable compounds within their VOs, mirroring the success observed in the domain of medicinal plants.

Conclusion

The GC–MS characterization of *O. syriacum* VO indicated the presence of 22 components, with thymol, carvacrol, and γ-terpinene being the most prevalent. The most dominant components in *C. serpyllifolium* VO were p-cymene, carvacrol, and terpinene. Furthermore, 23 chemicals were discovered in *T. capitata* VO, with carvone and pulegone being the predominant components. The VO compositions were different from those found in other geographic areas. According to the antifungal activity results, all VOs from the three Palestinian Thyme species used in this investigation demonstrated strong action. The VOs isolated from *O. syriacum* and *C. serpyllifolium* displayed the strongest antifungal action against all clinical and ATCC Candida strains tested. Furthermore, in vivo, studies are necessary to validate the anticandidal activity of these VOs.

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Availability of the data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. The datasets supporting the conclusions of this article are included in the manuscript. The raw data and materials of the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
The authors of the current work gave consent for publication to Dr. Mohammad Qadi.

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

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