

Antimicrobial activity and chemical composition of *Syringa vulgaris* L. essential oil and molecular docking simulation of its selected major chemical component

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Syringa vulgaris L. is a well-known ornamental plant used in traditional medicine, but its therapeutic properties and bioactive components have not been sufficiently investigated. Furthermore, there is a lack of detailed research on how the components of *Syringa vulgaris* essential oil (SVEO) interact at the molecular level with target proteins. This study aimed to evaluate the chemical composition and antimicrobial activity of SVEO *in vitro* and *in silico*. GC-MS identified 32 compounds. The most abundant compounds were identified as diethyl phthalate (54.296%), alpha-terpineol (24.141%), and gamma-terpineol (11.389%). SVEO was inactive against nearly all tested bacterial strains in the *in vitro* antibacterial assay but demonstrated varying levels of antifungal activity against yeasts (especially *Candida albicans*) and *Aspergillus* spp. Finally, the binding affinities of the three main components revealed significant potential to inhibit five target receptor proteins crucial to *Candida albicans*, as assessed using the AutoDock-Vina program, which helped determine the antifungal mechanism. SwissADME results for drug-like properties and toxicity prediction showed that these components met the rule of five and exhibited acceptable drug-like properties. Therefore, this study suggests that SVEO is a promising candidate, particularly for treating *Candida albicans* infections and addressing the growing issue of antifungal resistance.

Keywords: lilac oil, essential oil components, GC-MS, antibacterial activity, antifungal activity, prediction of drug similarity

Introduction

Antimicrobial resistance (AMR) is the ability of microbes to withstand the effects of drugs that were once effective against them. This resistance arises through mutations or the acquisition of resistance genes, leading microorganisms to become unresponsive to antimicrobial treatments. AMR poses risks to humans, animals, plants, and the environment¹. The resistance of key pathogens to standard treatments and the proliferation of multidrug-resistant microorganisms are increasing rapidly. Diseases once easily treated with antibiotics are now becoming difficult or impossible to cure. Consequently, the pool of effective drugs diminishes, making infections harder to manage. Additionally, many surgeries and immunosuppressive therapies depend on antibiotics to prevent and treat infections, so AMR threatens healthcare systems. Ineffective treatment accelerates disease spread, increasing the risk of severe illness and death. There is an urgent need for new drugs and alternative antimicrobial strategies².

Essential oils (EOs) are lipophilic, volatile secondary metabolites with a molecular weight of less than 300^{3,4}. They are natural mixtures whose chemical makeup and concentrations vary depending on factors such as geographic location, climate, extraction techniques, and the plant part used—such as flowers, leaves, stems, bark, fruits, or seeds. The main components in essential oils influence their biological activities^{3,5}. These oils and their constituents display various biological effects, including analgesic⁶ and anti-inflammatory⁷ properties, larvicidal activity⁸, antioxidant⁹, antifungal¹⁰, antibacterial¹¹, and antitumor¹² effects. Their antimicrobial properties are linked to the presence of volatile bioactive substances^{3,5}. Owing to these properties, plants and their essential oils have been used for diverse purposes since ancient times. They are used across industries such as agriculture, food, and cosmetics³. Of the roughly 3,000 known essential oils, about 300 are important to industries such as food, medicine, and cosmetics^{3,5}. They also feature in traditional and alternative medicine¹³.

The Oleaceae family comprises 25 genera and around 688 species of dicotyledonous flowering plants, widespread in tropical and temperate zones. Members of this family are economically valuable

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and popular in horticulture, with some species having medicinal uses¹⁴. *Syringa* spp. (lilac), Oleaceae, with 40 species, is mainly found in Southeastern Europe, Japan, China, and Himalayas¹⁵. These plants are low-maintenance, known for their fragrant, colorful flowers that thrive in drought-prone, sunny, and poor soils. While often cultivated as ornamentals in fields, rocky areas, and gardens, they are also used in perfume production due to their strong aroma^{14,16}. In traditional Chinese medicine, *Syringa* spp. are used to treat cough, cardiac ischemia, hepatitis with jaundice, diarrhea, conjunctivitis, bronchitis, and various other ailments. Their anti-inflammatory properties make them useful in managing rheumatoid arthritis, gout, rheumatism, and diabetes^{17,18}. Many traditional uses are supported by scientific evidence^{19,20}. Pharmacological research, both *in vitro* and *in vivo*, has shown that extracts and pure compounds from *Syringa* spp. possess significant hepatoprotective, anti-inflammatory, antimicrobial, antioxidant, antipyretic, pain-relief, anticancer, antiviral, cardioprotective, and immune-modulating activities²¹. This study aimed to investigate the chemical composition and antimicrobial activity of *Syringa vulgaris* essential oil (SVEO) against Gram-positive and Gram-negative bacteria, yeast, and *Aspergillus* spp. Additionally, the molecular docking and drug similarity properties of the three main components of SVEO were evaluated against target receptor proteins of critical importance for *Candida albicans* to identify the potential mechanisms of action associated with its antimicrobial activity.

Materials and Methods

Microorganisms

Clinical isolates and reference strains from the researcher's culture collection were used in the study. The reference Gram-positive bacteria included *Staphylococcus aureus* ATCC 29213 and ATCC 25923, *Enterococcus faecalis* ATCC 29212, and *Bacillus subtilis* ATCC 6633. The clinical Gram-positive bacterial isolates comprised *Enterococcus faecalis*, *Staphylococcus capitis*, *Staphylococcus epidermidis* (three isolates), and *Staphylococcus gallinarum*. The reference Gram-negative bacteria consisted of *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, *Pseudomonas aeruginosa* ATCC 10145 and ATCC 27853, *Salmonella* Typhimurium ATCC 51812, and *Salmonella* Enteritidis ATCC 13076. The clinical

Gram-negative bacteria used in the study were *Acinetobacter baumannii* (three isolates) and *Klebsiella pneumoniae*. The reference yeast cultures included *Candida albicans* ATCC 10231, *Candida albicans* ATCC 14053, *Candida albicans* ATCC 24433, *Candida albicans* ATCC 90028, *Candida parapsilosis* ATCC 22019, *Candida tropicalis* ATCC 1021, and *Cryptococcus neoformans* ATCC 90112. The clinical isolates included 19 *Candida albicans*. Additionally, the ochratoxin A-producing *Aspergillus carbonarius* PP264185²² and *Aspergillus niger* NRRL 321 cultures were also used.

Essential Oils

Syringa vulgaris EO was obtained from Kırıntı, in Kocaeli, Türkiye.

Determination of Essential Oil Volatile Component Composition

The volatile components of SVEO were analyzed using gas chromatography-mass spectrometry (GC-MS). The analyses were performed using a 7890A model gas chromatograph (Agilent Technologies) and a 5975C series mass spectrometer. A CP WAX 52 CB capillary column (50 m × 0.25 mm inner diameter, 0.2 µm film thickness) was employed to separate volatile components. Helium was selected as the carrier gas, with a flow rate of 1.2 mL/min. The GC temperature program was as follows: the initial temperature was maintained at 60°C for 2 minutes, after which the temperature increased at a rate of 2°C/min to reach 220°C, which was then held constant for 20 minutes. For the analysis, 100 µL of the sample was prepared by dissolving it in 1 mL of hexane and injected at a volume of 1 µL. The temperature of the injection unit was set at 240°C, while the detector temperature was maintained at 250°C. The mass spectrometer operated in electron impact (EI) mode at an energy level of 70 eV. Data integration was performed using MSDCHEM software²³.

In vitro Antimicrobial Activity Assays

Inoculum Preparation

For antimicrobial activity analysis, bacterial and yeast cultures were resuscitated in Tryptic Soy Agar (TSA) (Biolife, Italy) and Sabouraud Dextrose Agar (SDA) (Liofilchem, USA) at 36 ± 1°C for 18-24 hours. The cell density of the cultures was then adjusted to 0.5 McFarland using a McFarland densitometer (Biosan, DEN-1, Latvia) with physiological saline (0.85% w/v NaCl (Isolab, Germany))^{23,24}.

Aspergillus spp. isolates were cultivated on Potato Dextrose Agar (PDA) (Merck, Germany). These isolates were then transferred onto fresh PDA plates and incubated at 25°C for 7 to 10 days. To harvest the spores, 10 mL of sterile 0.1% v/v Tween 80 (Merck, Germany) solution was added to the medium, and the spores were scraped off with a Drigalski loop. The spore suspension was then transferred into a sterile tube. Antifungal activity tests were conducted using this freshly prepared spore suspension. The cell density of the cultures was then adjusted to 0.5 McFarland using a McFarland densitometer (Biosan, DEN-1, Latvia) with a sterile 0.1% v/v Tween 80 solution^{25,26}.

Determination of Antimicrobial Activity by Agar Well Diffusion Method

The agar well diffusion method was performed against bacteria as described by Özcan Ateş and Bican Süerdem²⁴, against yeast as described by Özcan Ateş and Kanbur²³, and against *Aspergillus* spp. as described by Özcan Ateş^{25,26}. Levofloxacin (5 mcg, Bioanalyze, Türkiye) and fluconazole (25 mcg, Himedia, India) antibiotic and antifungal discs were used as positive controls. Mueller Hinton Agar (MHA) (Difco, USA) medium was used for bacterial cultures, and Mueller-Hinton Agar + 2% Glucose, 0.5 µg/mL Methylene Blue Agar (MHA+GMB) (Himedia, India) plate was used for yeast cultures. A Potato Dextrose Agar (PDA) plate was used for *Aspergillus* spp. cultures.

The inoculum suspension prepared for bacteria and yeast was applied to the surface of dried MHA and MHA+GMB plates using a sterile cotton swab within 15 minutes of preparation. The spore suspension prepared for *Aspergillus* spp. was added to the dried PDA surface as 100 µL and spread with a Drigalski loop. Afterwards, 6 mm wells were drilled with a cork borer within 15 minutes, and 20 µL of SVEO was added to each well. The MHA and MHA+GMB media were incubated at 37°C for 24 hours, and the PDA plates were incubated at 25°C for 3-5 days. At the end of the incubation periods, zone diameters were measured using a digital caliper (KMP150, OEM, China). A well-diffusion assay was performed three times, and the data are presented as the mean (M) ± standard deviation (SD) using SPSS (v23.0, IBM Corp., Armonk, NY, USA).

Determination of Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal/Fungicidal Concentration (MBC or MFC)

The minimum inhibitory concentration (MIC) for bacteria was determined using the microdilution method in 96-well U-bottom plates as described in Özcan Ateş and Bican Süerdem²⁴. To ensure a homogeneous mixture of SVEO, 3% dimethyl sulfoxide (DMSO) (Isolab, Germany) was added to Mueller-Hinton Broth (MHB) (Biolife, Italy) medium. 100 µL of the medium containing double-layer SVEO and MHB were added to each well of the plate. Then, 100 µL of the inoculum suspension adjusted to 0.5 McFarland was added to the wells. The final volume in each well was 200 µL. The final concentrations of SVEO in MHB containing 3% DMSO were 40, 20, 10, 5, 2.5, and 1 µL/mL. MHB medium containing 40 µL/mL 3% DMSO was used as a negative control. 100 µL MHB containing 3% DMSO and 100 µL cell suspension were used as a positive control. Incubated at 37°C for 18-24 hours.

The MIC value for yeasts and *Aspergillus* spp. was determined according to Özcan Ateş and Kanbur²³ and Özcan^{25,26}. RPMI 1640 medium containing 0.2% glucose and 0.165 M MOPS (Himedia, India) was used in the study. 3% DMSO was added for homogeneous distribution of SVEO in the medium. Cell suspensions adjusted to 0.5 McFarland were diluted 1:1000. 100 µL of 2x SVEO and RPMI 1640 medium were added. Then, 100 µL of the suspension containing 1:1000 diluted cell suspension was added to the wells. Yeasts were incubated at 37°C for 24-48 hours, while *Aspergillus* spp. was incubated at 25°C for 3 days.

After incubation, a sterile 1% w/v 2,3,5-tetrazolium chloride solution (Merck, Germany) was added to the microplates, and the lowest concentration that did not exhibit a color change was determined as the MIC. After determining the MIC value, wells with no growth were inoculated into TSA for bacteria, SDA for yeast, and PDA for mould medium by the drip inoculation method, and the lowest concentration that did not show growth was determined as the minimum bactericidal/fungicidal concentration (MBC/MFC). The MFC/MIC ratio was used to interpret the SVEO's activity. Bacteriostatic or fungistatic agents when the MBC/MIC ratio is >4 and bactericidal or fungicidal agents when the MFC/MIC ratio is ≤4^{27,28,29}. The study was performed three times.

Effect of SVEO on Radial Growth of *Aspergillus* spp. Mycelium

This study was conducted in accordance with Özcan^{25,26}. To analyze the effect of SVEO on the radial growth of mold mycelium, *Aspergillus* spp. grew in PDA medium at 25 °C for 7-10 days. PDA media containing 3% DMSO were prepared at concentrations of MIC, 2x MIC, and 4x MIC and were poured into 60 mm diameter petri dishes. A single point was inoculated from the cultures grown in PDA medium in the middle of the petri dish using a needle loop. PDA media containing 3% DMSO was inoculated as a control. Petri dishes were incubated at 25 °C for 7 days, and the diameters of the colonies were measured after incubation. Zone diameters were measured at the end of the incubation period. The study was conducted three times. Radial growth inhibition was calculated using the following equation: $I\% = (C-T)/C \times 100$

C: Growth diameter (mm) in the control petri dish,
T: Growth diameter (mm) in the petri dish containing essential oil, I: Inhibition (%).

Molecular Docking Experiments**Protein Preparation**

Molecular docking operations were performed between the compounds detected in SVEO and the protein and enzyme structures found in *Candida albicans*. The detected protein structures were saved on "Protein Data Bank" (<https://www.rcsb.org>) with the extension ".pdb". Lanosterol 14a – demethylase (PDB ID: 5TZ1), Erg11 (PDB ID: 5V5Z), Methionine synthase (PDB ID: 4L61), SAP2 (PDB ID: 1EAG) and *Candida albicans* chitin synthase (PDB ID: AF-A0A1X0R3B0-F1-model_v4) protein files modeled using AlphaFold were reduced to the lowest level in terms of energy, non-essential water molecules and all complex-forming ligands were removed, polar hydrogen atoms were added to the receptors, and protein geometries were re-optimized. These preparation processes were carried out using "BIOVIA Dassault Systems"³⁰ and saved in ".pdb" format for final preparation for docking operations. The 'PDB' files prepared for interaction were converted to 'PDBQT' format using PyRx software³¹. They were adjusted according to the standard "AutoDock Vina" parameters³². Grid sizes were selected to maximize dimensions based on the atoms at the outermost points of each protein in every direction (x,y,z), and interactions were performed using the AutoDock Vina 1.1.2 tool with the 'blind docking' method.

Ligand Preparation

Among the volatile substances detected in the chemical composition of SVEO using GC-MS, the three ligands with the highest intensity were selected as alpha-terpineol, gamma-terpineol, and diethyl phthalate ligands. The ligands obtained from the National Center for Biotechnology Information (NCBI) "PubChem" were saved with the ".pdbqt" extension for the molecular docking process. They were adjusted according to the standard "AutoDock Vina" parameters³².

Molecular Docking Analysis of Three Major Compounds

Using the AutoDock Vina calculation tool via PyRx software, five proteins and three ligands were tested separately. Docking scores were calculated as predicted binding free energies (in kcal/mol)^{31,32}. The interactions of the resulting complexes were examined in BIOVIA, Discovery Studio program, and the resulting chemical bonds, protein surface structures, and amino acid residues interacting with ligand atoms were determined³⁰.

Drug Similarity (ADME) Calculation of Three Major Compounds

The drug similarity properties of the three ligands with the highest density among the volatile substances detected in the chemical composition of SVEO-Alpha-Terpeneol, Gamma-Terpeneol, and Diethyl Phthalate- were determined using the SwissADME online server³³. The results were analyzed in consideration of Lipinski's rule of five³⁴.

Results

GC-MS analysis of SVEO identified 33 components (Table 1). The dominant components were diethyl phthalate, alpha-terpineol, and gamma-terpineol at. Monoterpene alcohol made up a total of 41.2%, with alpha-terpineol at 24.14%, gamma-terpineol at 11.39%, beta-terpineol at 2.81%, and terpinene-1-ol at 1.15%. Sesquiterpenes, including junipene, alpha-longipinene, trans-caryophyllene, longicyclene, and cedrene, were present at a very low combined rate of 0.47%. Additionally, compounds with antifungal and antibacterial properties reported in the literature, such as eugenol, fenchyl alcohol, linalool, and isoborneol, were also detected at low concentrations. An examination of the oil's chemical profile revealed that terpineol derivatives constituted over 40% of the total, which may play a significant role in determining its potential antimicrobial activity. However, the high concentration of diethyl phthalate

Table 1 — Volatile component composition of *Syringa vulgaris* essential oil (SVEO)

Compounds	Retention Time	Abundance %
Diethyl phthalate	69.187	54.296
Alpha terpineol	36.958	24.141
Gamma-Terpineol	37.093	11.389
Beta terpineol	33.16	2.812
Terpinene 1-ol	30.07	1.154
Propylene glycol	31.293	1.154
Cis-beta-terpineol	35.938	1.077
Phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl	48.041	0.765
4-Terpineol	31.507	0.369
Junipene	29.342	0.345
Fenchyl alcohol	30.514	0.270
Dicyclopentadiene alcohol	46.405	0.245
Eugenol	60.23	0.219
Delta-terpineol	35.3750	0.179
Benzene, 1,2,4,5-tetramethyl-	40.743	0.177
Linalool	28.55	0.120
3,4-dimethylbenzyl isothiocyanate	39.032	0.118
8-hydroxy-1,4-cineole	26.901	0.100
Beta-citronellol	40.55	0.089
Alpha-iso-methyl ionone	44.592	0.089
Isoborneol	35.057	0.079
1,3-Dioxolane, 4-methy-2-phenyl	44.383	0.078
Dicyclopentadiene	46.537	0.070
Alpha-Longipinene	23.897	0.044
Trans-Caryophyllene	30.966	0.038
Camphor	26.561	0.035
Longicyclene	25.551	0.031
Terpinolen	45.275	0.026
Tricyclo[4.2.1.1(2,5)]dec-3-en-9-ol, stereoisomer	45.815	0.016
Linalyl acetate	28.966	0.013
Sativen	27.08	0.011
Cedrene	24.697	0.009

(54.29%) in the oil was considered contamination from the extraction process or a solvent residue, as it is not a natural component.

In this study, the broad-spectrum antimicrobial activity of SVEO was assessed using the agar well diffusion method. The results are presented in (Table 2). SVEO showed limited activity against Gram-negative bacteria. Notably, inhibition zones were observed for *A. baumannii* (clinical isolate 2685) (11.93 mm), *P. aeruginosa* ATCC 10145 (9.70 mm), *K. pneumoniae* ATCC 700603 (9.38 mm), *S. Enteritidis* ATCC 13076 (8.98 mm), *E. coli* ATCC 25922 (8.10 mm), and *S. Typhimurium* ATCC 51812 (7.65 mm). However, no inhibition zones were detected against *A. baumannii* (clinical isolates 1048 and 1132),

K. pneumoniae (clinical isolate 1042), and *P. aeruginosa* ATCC 27853. Among Gram-positive bacteria, *S. aureus* ATCC 29213 (13.63 mm) demonstrated the highest sensitivity. Significant inhibition zones were also observed in *B. subtilis* ATCC 6633 (10.24 mm) and *B. subtilis* (10.64 mm). However, the SVEO did not exhibit antibacterial activity against *E. faecalis*, *S. epidermidis*, and *S. gallinarum*.

The most striking result of the study was that SVEO exhibited significant antimicrobial activity against yeast species. Inhibition zones were noted to range from 9.94 to 26.99 mm in both clinical isolates and reference strains of *C. albicans*. However, no activity was detected against the tested *C. parapsilosis* and *C. tropicalis*. As a result, they formed a zone of inhibition like that of an antifungal agent. These results demonstrate that the anticandidal effect of the SVEO is much stronger than its antibacterial activity. Antifungal activity was also detected against *A. carbonarius* (15.62 mm) and *A. niger* (10.17 mm).

MIC and MBC/MFC values of SVEO were determined using the microdilution method against tested microorganisms for which an inhibition zone was detected (Table 3). Based on MIC and MBC values, it was determined that it exhibited bactericidal activity against *E. coli*, *K. pneumoniae*, and *Salmonella* spp. due to an MBC/MIC ratio of ≤ 4 . However, very high MBC values ($>40 \mu\text{L/mL}$) were observed in *P. aeruginosa*, *B. subtilis*, and *S. aureus*, indicating only bacteriostatic activity. For the *A. baumannii* isolate, it was not possible to determine whether the effect was bactericidal or bacteriostatic due to an MIC value of greater than $40 \mu\text{L/mL}$. MIC values for *C. albicans* clinical isolates and reference strains were generally found to be in the range of $0.125\text{--}0.25 \mu\text{L/mL}$, and MFC values were found to be in the range of $0.125\text{--}0.5 \mu\text{L/mL}$. An MFC/MIC ratio of ≤ 2 indicated that SVEO had significant fungicidal activity against *C. albicans*. SVEO was found to be fungistatic, as MIC values were $40 \mu\text{L/mL}$ and MFC values were greater than $40 \mu\text{L/mL}$ for both *A. carbonarius* and *A. niger*.

The study also examined how SVEO affects the radial growth of *Aspergillus* spp. During the assessment of radial growth inhibition by SVEO at MIC, $2\times$ MIC, and $4\times$ MIC concentrations, measurements were taken. The results of radial growth inhibition for the *Aspergillus* spp. are shown in (Table 4). It was found that SVEO enhanced the percentage inhibition of radial growth in the *Aspergillus* spp.

Table 2 — Inhibition zones (in mm) determined by the agar well diffusion method of *Syringa vulgaris* essential oil (SVEO)

	Microorganisms	Inhibition zone (mm)		
		SVEO	Levofloxacin	Fluconazole
Gram negative bacteria	<i>Acinetobacter baumannii</i> (clinical isolate 1048)	6.00 ± 0.01	36.63 ± 0.16	-
	<i>Acinetobacter baumannii</i> (clinical isolate 1132)	6.00 ± 0.01	6.00 ± 0.01	-
	<i>Acinetobacter baumannii</i> (clinical isolate 2685)	11.93 ± 0.85	6.00 ± 0.01	-
	<i>Escherichia coli</i> ATCC 25922	8.10 ± 0.31	26.94 ± 1.86	-
	<i>Klebsiella pneumoniae</i> (clinical isolate 1042)	6.00 ± 0.01	24.12 ± 0.24	-
	<i>Klebsiella pneumoniae</i> ATCC 700603	9.38 ± 0.68	19.85 ± 1.36	-
	<i>Pseudomonas aeruginosa</i> ATCC 10145	9.70 ± 0.58	31.81 ± 0.89	-
	<i>Pseudomonas aeruginosa</i> ATCC 27853	6.00 ± 0.01	33.46 ± 1.11	-
	<i>Salmonella</i> Enteritidis ATCC 13076	8.98 ± 0.58	25.60 ± 1.65	-
	<i>Salmonella</i> Typhimurium ATCC 51812	7.65 ± 0.40	20.53 ± 2.79	-
	Gram positive bacteria	<i>Bacillus subtilis</i>	10.64 ± 1.58	31.53 ± 0.92
<i>Bacillus subtilis</i> ATCC 6633		10.24 ± 0.48	25.52 ± 0.50	-
<i>Enterococcus faecalis</i> (clinical isolate 1075)		6.00 ± 0.01	29.39 ± 0.60	-
<i>Enterococcus faecalis</i> ATCC 29212		6.00 ± 0.01	12.57 ± 0.34	-
<i>Staphylococcus capitis</i> (clinical isolate 2670)		6.00 ± 0.01	6.00 ± 0.01	-
<i>Staphylococcus epidermidis</i> (clinical isolate 2657)		6.00 ± 0.01	6.00 ± 0.01	-
<i>Staphylococcus epidermidis</i> (clinical isolate 2666)		6.00 ± 0.01	29.25 ± 2.36	-
<i>Staphylococcus epidermidis</i> (clinical isolate 2671)		6.00 ± 0.01	6.00 ± 0.01	-
<i>Staphylococcus aureus</i> ATCC 25923		7.90 ± 0.85	26.82 ± 0.33	-
<i>Staphylococcus aureus</i> ATCC 29213		13.63 ± 2.21	29.96 ± 0.10	-
<i>Staphylococcus gallinarum</i> (clinical isolate 1093)		6.00 ± 0.01	35.75 ± 0.42	-
Yeast	<i>Candida albicans</i> (clinical isolate 1)	26.87 ± 1.42	-	38.45 ± 1.73
	<i>Candida albicans</i> (clinical isolate 2)	22.64 ± 4.03	-	35.59 ± 0.64
	<i>Candida albicans</i> (clinical isolate 3)	23.67 ± 1.55	-	41.30 ± 0.91
	<i>Candida albicans</i> (clinical isolate 4)	18.94 ± 1.35	-	35.19 ± 0.99
	<i>Candida albicans</i> (clinical isolate 5)	23.27 ± 2.10	-	34.11 ± 0.88
	<i>Candida albicans</i> (clinical isolate 6)	21.40 ± 2.35	-	39.60 ± 1.91
	<i>Candida albicans</i> (clinical isolate 7)	26.96 ± 1.26	-	37.15 ± 0.81
	<i>Candida albicans</i> (clinical isolate 8)	21.82 ± 1.50	-	26.23 ± 0.52
	<i>Candida albicans</i> (clinical isolate 9)	18.03 ± 1.49	-	34.42 ± 0.87
	<i>Candida albicans</i> (clinical isolate 10)	26.99 ± 5.54	-	31.74 ± 1.44
	<i>Candida albicans</i> (clinical isolate 11)	24.52 ± 1.49	-	30.03 ± 0.73
	<i>Candida albicans</i> (clinical isolate 12)	25.35 ± 2.15	-	42.03 ± 0.50
	<i>Candida albicans</i> (clinical isolate 13)	20.66 ± 1.27	-	41.88 ± 1.01
	<i>Candida albicans</i> (clinical isolate 14)	19.79 ± 0.82	-	26.65 ± 0.38
	<i>Candida albicans</i> (clinical isolate 15)	20.22 ± 0.65	-	39.79 ± 0.65
	<i>Candida albicans</i> (clinical isolate 16)	20.63 ± 0.62	-	42.17 ± 0.59
	<i>Candida albicans</i> (clinical isolate 17)	20.45 ± 1.05	-	33.67 ± 0.99
	<i>Candida albicans</i> (clinical isolate 18)	18.71 ± 1.36	-	38.39 ± 0.41
	<i>Candida albicans</i> (clinical isolate 19)	18.86 ± 0.93	-	35.30 ± 0.32
<i>Candida albicans</i> ATCC 10231	17.97 ± 1.20	-	36.83 ± 0.69	
<i>Candida albicans</i> ATCC 14053	18.34 ± 1.98	-	43.74 ± 5.94	
<i>Candida albicans</i> ATCC 24433	9.94 ± 0.72	-	42.04 ± 6.87	
<i>Candida albicans</i> ATCC 90028	10.21 ± 0.41	-	41.84 ± 6.02	
<i>Candida parapsilosis</i> ATCC 22019	6.00 ± 0.01	-	41.59 ± 5.32	
<i>Candida tropicalis</i> ATCC 1021	6.00 ± 0.01	-	35.66 ± 4.39	
<i>Cryptococcus neoformans</i> ATCC 90112	6.00 ± 0.01	-	35.40 ± 0.84	
Mould	<i>Aspergillus carbonarius</i> PP264185	15.62 ± 1.27	-	90.00 ± 0.01
	<i>Aspergillus niger</i> NRRL 321	10.17 ± 2.57	-	90.00 ± 0.01

-: not determined.

For *in silico* analysis, SVEO was evaluated against *C. albicans* due to its high anticandidal and fungicidal activity. Molecular docking operations were performed

to obtain 135 different affinity/binding free energy scores from the interactions of target receptor proteins (Lanosterol 14a – demethylase (PDB ID: 5TZ1), Erg11

Table 3 — MIC and MBC or MFC ($\mu\text{L}/\text{mL}$) values were determined by the microdilution method of *Syringa vulgaris* essential oil (SVEO)

	Microorganisms	MIC	MBC or MFC	MBC/MIC or MFC/MIC
Gram negative bacteria	<i>Acinetobacter baumannii</i> (clinical isolate 2685)	>40	>40	-
	<i>Escherichia coli</i> ATCC 25922	1	2	2
	<i>Klebsiella pneumoniae</i> ATCC 700603	1	2	2
	<i>Pseudomonas aeruginosa</i> ATCC 10145	1	>40	>40
	<i>Salmonella</i> Enteritidis ATCC 13076	0.5	2	4
	<i>Salmonella</i> Typhimurium ATCC 51812	1	2	2
Gram positive bacteria	<i>Bacillus subtilis</i>	0.5	>40	>80
	<i>Bacillus subtilis</i> ATCC 6633	1	>40	>40
	<i>Staphylococcus aureus</i> ATCC 25923	1	>40	>40
	<i>Staphylococcus aureus</i> ATCC 29213	1	>40	>40
	<i>Candida albicans</i> (clinical isolate 1)	0.25	0.5	2
Yeast	<i>Candida albicans</i> (clinical isolate 2)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 3)	0.125	0.125	1
	<i>Candida albicans</i> (clinical isolate 4)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 5)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 6)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 7)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 8)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 9)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 10)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 11)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 12)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 13)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 14)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 15)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 16)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 17)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 18)	0.25	0.5	2
	<i>Candida albicans</i> (clinical isolate 19)	0.25	0.5	2
	Mould	<i>Candida albicans</i> ATCC 10231	0.25	0.5
<i>Candida albicans</i> ATCC 14053		1	2	2
<i>Candida albicans</i> ATCC 24433		1	2	2
<i>Candida albicans</i> ATCC 90028		1	2	2
<i>Aspergillus carbonarius</i> PP264185		40	>40	>40
	<i>Aspergillus niger</i> NRRL 321	40	>40	>40

(PDB ID: 5V5Z), Methionine synthase (PDB ID: 4L61), SAP2 (PDB ID: 1EAG) and *C. albicans* chitin synthase (PDB ID: AF-A0A1X0R3B0-F1-model_v4) which are vital for *C. albicans*, with three main volatile compounds (α -terpineol, γ -terpineol and diethyl phthalate) detected in SVEO. The highest scores of each interaction were compared. Diethyl phthalate was the prominent ligand that docked with the highest free binding energy to 4 out of 5 target receptors. Additionally, all ligands achieved the highest scores. They obtained their scores from the interaction with chitin synthase (Table 5).

The docking results were visualized with 3D modeling, and the topological and hydrophobic

properties of the binding sites were examined (Fig 1). The chemical interactions between the ligand and the protein are illustrated in a 2D diagram, and the specific atom that bonds with each amino acid residue is also indicated (Fig 2).

Drug-like properties of the three ligands detected in the most concentrated amounts in SVEO were determined using the SwissADME online server. When the results were examined in consideration of Lipinski's rule of 5, no violations were found³⁵. The "boiled egg" results (Fig 3) showed that all ligands could be absorbed in the body and could cross the blood-brain barrier³⁵. The disadvantage was that none of the ligands were P-glycoprotein (P-gp) substrates.

Table 4 — Radial growth inhibition rate (in %)

Concentrations of SVEO	<i>A. carbonarius</i> PP264185	<i>A. niger</i> NRRL 321
MIC (40 µL/mL)	44.23 ± 2.38	34.17 ± 1.67
MIC x 2 (80 µL/mL)	63.68 ± 2.71	41.93 ± 0.62
MIC X 4 (160 µL/mL)	74.79 ± 1.08	61.45 ± 0.61

Table 5 — Highest scores, affinity table

(kcal/mol)	Alpha-Terpineol	Gamma-Terpineol	Diethyl Phthalate
5TZ1	-6.6	-6.4	-7.3
5V5Z	-6.8	-6.2	-7.3
4L61	-7.1	-6.8	-6.6
1EAG	-5.9	-5.6	-6.6
AF*	-7.3	-6.9	-7.4

Lanosterol 14a – demethylase (PDB ID: 5TZ1), Erg11 (PDB ID: 5V5Z), Methionine synthase (PDB ID: 4L61), SAP2 (PDB ID: 1EAG) and *Candida albicans* chitin synthase (PDB ID: AF-A0A1X0R3B0-F1-model_v4)

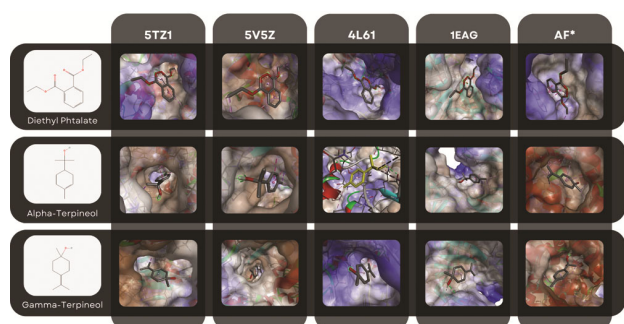


Fig. 1 — 3D visualization of structures with top affinity scores shows the protein surface (Lanosterol 14a – demethylase (PDB ID: 5TZ1), Erg11 (PDB ID: 5V5Z), Methionine synthase (PDB ID: 4L61), SAP2 (PDB ID: 1EAG) and *Candida albicans* chitin synthase (PDB ID: AF-A0A1X0R3B0-F1-model_v4)) adjusted for hydrophobicity: blue indicates more hydrophilic areas, brown highlights hydrophobic regions, and white marks neutral zones. Ligands bind to both hydrophobic and hydrophilic active sites, forming stable complexes. In the chitin synthase (AF*) protein, ligands occupy a large, deep binding pocket, indicating strong compatibility and high affinity for this target.

The property of being a P-gp substrate is an important parameter in terms of the ligand not being excreted from the body and causing toxic effects³⁶.

Discussion

This study evaluated the chemical composition, *in vitro* antimicrobial activity, and *in silico* molecular interactions of the essential oil of *Syringa vulgaris* L. Previous studies have shown that *Syringa* species contain a variety of metabolites, including iridoids, lignans, phenylethanoids, glycosides, and some organic acids^{15,16}. Varga *et al.* identified a total of 33 phenolic compounds in methanolic extracts of

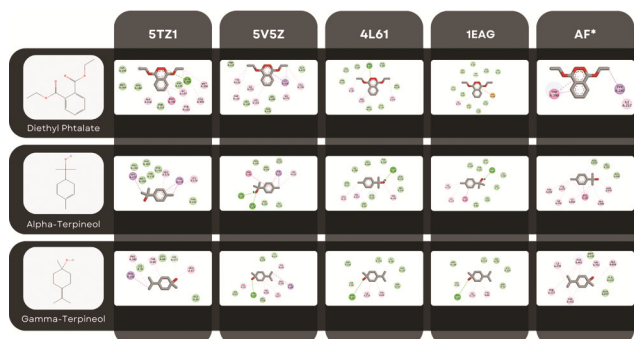


Fig. 2 — 2D diagram illustrates the structures with the highest affinity scores. It shows interactions between target receptor amino acids and ligand atoms. These interactions include hydrogen bonds (green dashed lines), π - π interactions (light pink/purple dashed lines), π -alkyl interactions (orange dashed lines), halogen bonds (light blue dashed lines), ionic bonds (red dashed lines), hydrophobic contacts (represented by gray or light green semicircles), and van der Waals contact surfaces (light gray areas). The data indicates that α -terpineol and γ -terpineol mainly interact with hydrophobic amino acids, whereas diethyl phthalate forms more stable binding conformations owing to its additional hydrogen-bonding groups. (Lanosterol 14a – demethylase (PDB ID: 5TZ1), Erg11 (PDB ID: 5V5Z), Methionine synthase (PDB ID: 4L61), SAP2 (PDB ID: 1EAG) and *Candida albicans* chitin synthase (PDB ID: AF-A0A1X0R3B0-F1-model_v4))

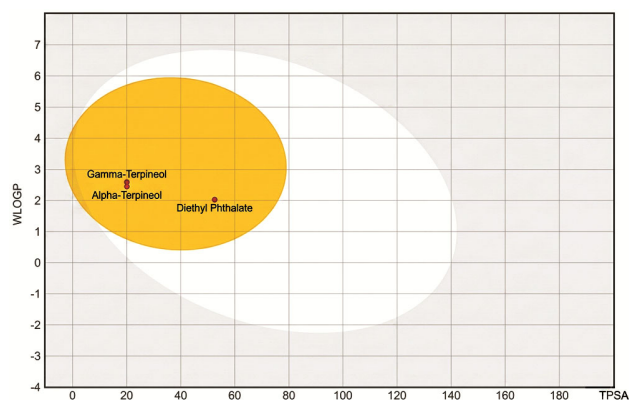


Fig. 3 — “Boiled egg” graph obtained from the SwissADME online server. The ligand is marked in red, indicating that it is not predicted to be a P-gp substrate.

S. vulgaris bark and leaves, including 15 secoridoids, six phenylpropanoids, three flavonoids, three lignans, and six low-molecular-weight phenols²⁰. Gecer identified 57 compounds in the EO obtained from the flowers of *S. vulgaris* L., the main components of which were linalool (26.34%), α -terpineol (10.84%), trans geraniol (9.83%), α -bisabolol (4.50%), cis-nerol acetate (5.28%), and lavandulyl acetate (4.32%)³⁷. Different studies have investigated the components of SVEO, revealing a complex mixture of bioactive compounds. In this study, 32 volatile compounds

were identified in the SVEO. Listed from highest to lowest: diethyl phthalate, α -terpineol, γ -terpineol, β -terpineol, terpinen-1-ol, propylene glycol, cis- β -terpineol, phenol (2,6-bis(1,1-dimethyl ethyl)-4-methyl), 4-terpineol, junipen, fenchyl alcohol, dichlorocyclopentadiene alcohol, eugenol, delta-terpineol, benzene (1,2,4,5-tetramethyl), linalool, 3,4-dimethyl benzyl isothiocyanate, 8-hydroxy-1,4-cineole, β -citronellol, α -iso-methyl ionone, isoborneol, 1,3-dioxolane (4-methyl-2-phenyl), dichlorocyclopentadiene, α -longipinene, trans-caryophyllene, camphor, longicyclene, Terpinolene, tricyclo[4.2.1.1(2.5)]dec-3-en-9-ol stereoisomer, linalyl acetate, sativene, and cedrene were found. Similar compounds were identified in the study, as well as different components found in the literature. This is because the chemical composition of EOs is affected by factors such as geographical location, climate, and extraction methods.

The *in vitro* antimicrobial activity of SVEO was determined to be bactericidal against *E. coli*, *K. pneumoniae*, and *Salmonella* spp., as indicated by MIC and MBC values related to its antibacterial activity. It exhibited bacteriostatic activity against *P. aeruginosa*, *B. subtilis*, and *S. aureus*. No significant activity was observed against *A. baumannii* strains. This result suggests that the effect of the SVEO against bacteria is species and structure-dependent, and that outer membrane permeability, especially in Gram-negative bacteria, may limit its effectiveness. However, SVEO was determined to have strong anticandidal activity, especially against *C. albicans*, and to have fungicidal activity. Only a fungistatic effect was detected on *Aspergillus* spp., indicating that antifungal susceptibility varies species-specifically. There are limited studies on the antimicrobial activity of SVEO in literature. Kenan *et al.* reported that methanol extracts of *S. vulgaris* flowers did not determine any antimicrobial activity against the tested bacteria and yeasts (*S. epidermidis* ATCC 12228, *B. subtilis* ATCC 6633, *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, *S. Typhimurium* ATCC 14028, *E. coli* ATCC 8739, *E. faecalis* ATCC 29212, and *C. albicans* ATCC 1029)³⁸. In another study, *S. vulgaris* methanol extract exhibited anti-quorum-sensing activity on *Cromobacterium violaceum* CV026 with inhibition zones of 10.5 ± 1.0 mm and inhibited $100.0 \pm 0.0\%$ violacein production in *C. violaceum* CV12472²¹. Additionally, two separate studies investigated the antifungal activity of compounds derived from *Syringa* spp. In the first of

these studies, Bao *et al.* isolated a new sesquiterpene called syringinol in the EO of the *Syringa pinnatifolia* Hemsl. var. *Alashanensis* plant body. They determined that two previously unknown compounds isolated from this plant for the first time exhibited inhibition zones of 16.34 ± 0.24 and 19.32 ± 0.18 mm against an isolate of *A. niger*³⁹. Ao *et al.* reported that two new sesquiterpenes, guai-9-en-4 β -ol (1) and 14,15-dinorguai-1,11-dien-9,10-dione (2), from the stem of *S. pinnatifolia* had inhibition zone diameters of 13.20 and 11.53 mm against the *A. niger* isolate, respectively⁴⁰. In the study, SVEO exhibited limited antimicrobial activity but strong anticandidal activity. It was thought that the main components of SVEO, α -terpineol, γ -terpineol, and diethyl phthalate, may be related to antimicrobial activity. Previous studies have reported that the oxygenated monoterpenes α - and γ -terpineol disrupt membrane structure, increase cell permeability in microorganisms, inhibit metabolic processes, and exhibit fungicidal effects, particularly against fungi⁴¹⁻⁴⁴.

Studies on the antifungal activity and chemical profiles of other species in the Oleaceae family are also found in the literature. Al-Rimavi *et al.* stated that the antifungal activity of *Olea europaea* originates from oleuropein, specific to the leaf extract⁴⁵. Vural *et al.* reported that the main components of dried *O. europaea* leaf EOs are α -pinene ($9.82 \pm 0.33\%$), benzyl alcohol ($8.83 \pm 0.27\%$), phenethyl alcohol ($8.52 \pm 0.25\%$), 2-monopalmitin ($8.13 \pm 0.28\%$), palmitic acid ($5.53 \pm 0.41\%$), octadecanoic acid 2,3-dihydroxypropylester ($5.84 \pm 0.42\%$), phytol ($4.22 \pm 0.17\%$), and benzaldehyde ($4.21 \pm 0.38\%$), and that it exhibits antifungal activity against *C. albicans*⁴⁶. *O. europaea* contains phenolic compounds, particularly those called secoiridoids⁴⁷. Their mechanisms of action differ because *Syringa* contains monoterpene alcohols, such as oleuropein, in its chemical profile, whereas these are either absent or present in small amounts in other species. *Jasminum* species are another member. Studies by *Jasminum pubescens* (Retz.) Willd. have determined that EOs obtained from the flowers and leaves contain 50.8% and 58.2% non-terpene derivatives⁴⁸. Thaweboon *et al.* on the other hand, determined that *Jasminum sambac* flower EOs provided an inhibition zone of 13-26 mm against *C. albicans* ATCC 10231, *C. glabrata* ATCC 90030, *C. krusei* ATCC 6258, *C. parapsilosis* ATCC 22019, *C. pseudotropicalis* (clinical isolate), *C. stellatoidia* (clinical isolate), and *C. tropicalis* (clinical isolate), with MIC values varying between 0.19% and 0.78%

(v/v)⁴⁹. Similar to other studies on members of the Oleaceae family, *S. vulgaris* exhibit anticandidal activity due to their unique chemical composition. Moreover, Martorano-Fernandes *et al.* reported MIC values of 312.5 µg/mL against *C. albicans* ATCC 90028 and 40 µg/mL against *C. krusei*, indicating that α -terpineol has an inhibitory effect against *Candida* species⁵⁰. In particular, SVEO, which contains monoterpene alcohols such as α -, β -, and γ -terpineol, exhibits strong antifungal activity⁴⁴. Clinically, this information provides an alternative to antifungal agents and enhances the possibility of combining different treatments to improve outcomes.

Diethyl phthalate was identified as the primary compound in SVEO. It is a less frequently reported compound that can form strong hydrophobic interactions with proteins due to its lipophilic structure, which stands out in the analysis⁵¹⁻⁵³. However, phthalic acid esters have been identified not only in organic solvent extracts, root secretions, and essential oils of numerous different plant species, but also isolated and purified from various algae, bacteria, and fungi. Studies have generally found them in plant-derived EOs⁵⁴. In this study, all controls were performed during the chemical composition determination phase. Therefore, considering the amount, it suggests that diethyl phthalate is a component of the SVEO, rather than an analytical contamination.

Molecular docking studies support these findings. In analyses against target proteins critical to *C. albicans* (lanosterol 14 α -demethylase, Erg11, methionine synthase, SAP2, and chitin synthase), diethyl phthalate exhibited the highest binding energy among the three major compounds. A binding score of -7.4 kcal/mol, particularly with chitin synthase, suggests that this compound may interfere with fungal cell wall biosynthesis. α - and γ -terpineol also achieved high binding scores, indicating that the chemical composition revealed by GC-MS data supports antifungal activity at the molecular level. However, *in silico* analysis results are predictive, and further biochemical tests and *in vivo* studies are needed to confirm the mechanisms of action.

SwissADME predictions revealed that all three compounds did not violate Lipinski's rule of five and therefore possessed "drug-like" properties. Furthermore, according to the "hard-boiled egg" model, all compounds are bioabsorbable and can cross the blood-brain barrier, providing a pharmacokinetic advantage. However, their lack of P-glycoprotein substrate can be considered a

disadvantage in terms of toxicity and elimination^{34,35,36}. Therefore, *in vivo* verification of toxicity, bioavailability, and therapeutic efficacy is necessary. Thus, the data obtained are preliminary information, and more comprehensive studies are needed for clinical implications.

Conclusions

This study determined the chemical composition of *Syringa vulgaris* L. essential oil (SVEO) by GC-MS and assessed its biological activity via *in vitro* antibacterial and antifungal tests. GC-MS results identified diethyl phthalate, α -terpineol, and γ -terpineol as the main components of the SVEO. *In vitro* antimicrobial tests showed that SVEO exhibited limited antibacterial activity against both Gram-positive and Gram-negative bacteria but demonstrated significant antifungal activity against *Candida albicans*. Molecular docking analyses indicated that the main components of SVEO have strong binding affinities for key target proteins in *C. albicans*, aligning with experimental antifungal results. Additionally, SwissADME analyses suggested that these components could possess drug-like properties. These results point to SVEO as a promising candidate for the development of natural antifungal agents. Nonetheless, further work to improve its efficacy, assess toxicity, and perform *in vivo* validation is necessary.

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Conflicts of Interest

The author declares no conflicts of interest.

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