ATATÜRK ÜNİVERSİTESİ YAYINLARI
ATATURK UNIVERSITY PUBLICATIONS

Research Article / Araştırma Makalesi DOI:10.62425/crihs.1776763

GC–MS Profile, Antimicrobial Activity, and In Silico ADMET Evaluation of Major Constituents from *Pogostemon cablin* (Patchouli) and *Juniperus communis* (Juniper)

Pogostemon cablin (Paçuli) ve *Juniperus communis* (Ardıç) Esansiyel Yağlarının GC–MS Profili, Antimikrobiyal Aktivitesi ve Majör Bileşenlerinin In Silico ADMET Değerlendirmesi

Leyla GÜVEN [1]
Hayrunisa HANCI [2]
[1] Atatürk University, Faculty of Pharmacy, Department of Pharmaceutical Botany, Erzurum, Türkiye
[2] Atatürk University, Faculty of Pharmacy, Department of Pharmaceutical Microbiology, Erzurum, Türkiye

ABSTRACT

Objective: This study aimed to investigate the antimicrobial potential of essential oils obtained from *Pogostemon cablin (patchouli) and Juniperus communis (juniper)*, to identify their major phytoconstituents through GC–MS analysis, and to evaluate the pharmacokinetic properties of the dominant compounds using in silico ADMET.

Methods: Essential oils were analyzed by GC–MS. Antimicrobial activity was evaluated against *Staphylococcus aureus*, *Escherichia coli, Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* using disc diffusion method. In silico analyses (BOILED-Egg and bioavailability radar models) were employed to predict gastrointestinal absorption, blood–brain barrier penetration, and drug-likeness features of the major compounds.

Results: *Chavibetol, caryophyllene* and *linalool* were determined as major compounds for *P. cablin*; methyl salicylate, (-)-terpinen-4-ol and p-cymene were determined as major compounds for *J. communis*. According to the study results, the essential oils from *P. cablin* and *J. communis* exhibited the best antimicrobial activity against *S. aureus*, while both essential oils were ineffective against Gram-negative bacteria. In the BOILED-Egg model, chavibetol and linalool were located in the yellow region (high gastrointestinal absorption and P-gp–), while caryophyllene and linalool were located in the pink region of the bioavailability radar. For *J. communis*, all three major compounds were located in the yellow region (P-gp–), while *(-)-terpinen-4-ol* and *p-cymene* were located in the pink region of the radar, demonstrating optimal oral bioavailability.

Conclusion: Both *P. cablin* and *J. communis* essential oils exhibited potent antibacterial activity against *S. aureus*, but no significant effect was observed against Gram-negative species. GC–MS analysis and ADMET predictions revealed that the major phytochemicals possess promising pharmacokinetic properties for advanced drug development. In order to more clearly demonstrate the antimicrobial activities of these essential oils, it would be appropriate to conduct further studies using more bacterial species and to determine minimum inhibitory concentration values.

Keywords: ADMET, antimicrobial activity, essential oil, *Juniperus communis, Pogostemon cablin*

ÖZ

Amaç: Bu çalışma, Pogostemon cablin (paçuli) ve Juniperus communis (ardıç) türlerinden elde edilen esansiyel yağların antimikrobiyal potansiyelini araştırmayı, GC–MS analizi ile majör fitobileşenlerini tanımlamayı ve baskın bileşiklerin farmakokinetik özelliklerini in silico ADMET kullanarak değerlendirmeyi amaçlamıştır.

Yöntemler: Esansiyel yağlar GC–MS ile analiz edilmiştir. Antimikrobiyal aktivite, *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* ve *Pseudomonas aeruginosa* üzerinde disk difüzyon yöntemiyle test edilmiştir. Majör bileşiklerin gastrointestinal emilimini, kan-beyin bariyeri penetrasyonunu ve ilaç benzerlik özelliklerini tahmin etmek için in silico analizler (BOILED-Egg ve biyoyararlanım radar modelleri) kullanıldı.

Bulgular: *P. cablin* için *chavibetol, karyofillen* ve *linalool*; *J. communis* için metil salisilat, (-)-terpinen-4-ol ve p-simen majör bileşikler olarak belirlenmiştir. Çalışma sonuçlarına göre *P. cablin* ve *J. communis* uçucu yağları en iyi antimikrobiyal aktiviteyi *S. aureus*'a karşı gösterirken her iki uçucu yağın da Gram-negatif bakterilere etkisiz olduğu belirlenmiştir. BOILED-Egg modelinde chavibetol ve linalool sarı bölgede (yüksek gastrointestinal absorbsiyon ve P-gp–) konumlanırken; karyofillen ve linalool biyoyararlanım radarının pembe bölgesinde yer almıştır. *J. communis* için üç majör bileşiğin tümü sarı bölgede (P-gp–) konumlanırken, (-)-terpinen-4-ol ve p-simen radarın pembe bölgesinde yer alarak optimal oral biyoyararlanım göstermiştir.

Sonuç: Hem *P. cablin* hem de *J. communis* esansiyel yağları *S. aureus*'a karşı güçlü antibakteriyel aktivite göstermiş, ancak Gram-negatif türlerde anlamlı bir etki gözlenmemiştir. GC–MS analizi ve ADMET öngörüleri, majör fitobileşenlerin ileri ilaç geliştirme için umut verici farmakokinetik özelliklere sahip olduğunu ortaya koymuştur. Bu esansiyel yağların antimikrobiyal etkinliklerinin daha net ortaya koyulabilmesi için ise daha fazla bakteri türü kullanarak minimum inhibitör konsantrasyon değerlerinin de belirlenebileceği ileri çalışmaların yapılması uygun olacaktır.

Anahtar Kelimeler: ADMET, antimikrobiyal aktivite, esansiyel yağlar, *Juniperus communis*, *Pogostemon cablin*

Geliş Tarihi/Received 03.09.2025
Kabul Tarihi/Accepted 30.10.2025
Yayın Tarihi/Publication Date 02.11.2025

Sorumlu Yazar/Corresponding author: Hayrunisa Hancı
E-mail: hayrunisa.hanci@atauni.edu.tr
Cite this article: Güven, L., & Hancı, H. (2025). GC–MS Profile, Antimicrobial Activity, and In Silico ADMET Evaluation of Major Constituents from *Pogostemon cablin* (Patchouli) and *Juniperus communis* (Juniper). *Current Research in Health Sciences*, *2*(3), 111-122.

Introduction

Since ancient times, plants and their derivatives have played a central role in human health care, largely due to their pharmacological activities, low toxicity, and accessibility Among natural products, essential oils (EOs) have attracted particular attention as multifunctional agents with strong antimicrobial, antioxidant, and anti-inflammatory activities. The increasing prevalence of multidrug-resistant pathogens, including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella spp.*, and *Escherichia coli*, has highlighted the limitations of conventional antibiotics and emphasized the urgent need for new alternatives of natural origin (Chouhan et al., 2017). In this regard, EOs have been extensively investigated and are now considered valuable candidates not only for the treatment of infectious diseases but also for their potential applications in the food, pharmaceutical, and cosmetic industries (Murbach Teles Andrade et al., 2014).

In addition to their well-documented antibacterial effects, EOs demonstrate antifungal, antiviral, antiparasitic, and antitumor properties, while their terpenoid and phenolic constituents confer potent radical-scavenging activity, which may help in the prevention of oxidative stress–related disorders such as neurodegenerative diseases and cancer (Chouhan et al., 2017). Furthermore, their incorporation into food systems has been shown to prolong shelf life and preserve organoleptic quality, thereby supporting the growing global trend toward replacing synthetic preservatives with natural bioactive compounds (Murbach Teles Andrade et al., 2014). Thus, EOs represent an important interface between traditional medicine and modern scientific applications, offering promising perspectives in addressing both health and food safety challenges.

Pogostemon cablin Benth. (patchouli), a member of the Lamiaceae family, has been used for centuries due to its preservative and therapeutic properties. In Traditional Chinese Medicine (TCM), it has been applied since the Eastern Han dynasty for the treatment of colds, fever, headache, nausea, and diarrhea (Junren et al., 2021) Today, its essential oil is widely employed in perfumes, soaps, and cosmetic industries, while in aromatherapy it is valued for alleviating stress, depression, and appetite disorders (Swamy & Sinniah, 2015). Phytochemical investigations have identified more than 140 compounds from *P. cablin*, with patchouli alcohol, α- and β-patchoulene, α-bulnesene, seychellene, pogostone, and eugenol reported as major constituents (Silva-Filho et al., 2016). These phytochemicals have been associated with multiple biological activities, including antioxidant, antimicrobial, anti-inflammatory, analgesic, antitumor, antidiabetic, and immunomodulatory effects. Several pharmacological studies provide evidence supporting the traditional uses of patchouli essential oil, indicating that its broad pharmacological potential is largely attributable to its major constituents (Junren et al., 2021; Silva-Filho et al., 2016; Swamy & Sinniah, 2015).

Juniperus communis L. (Cupressaceae), commonly known as common juniper, is a coniferous shrub widely distributed throughout the Northern Hemisphere. Its dried bluish-black cones, referred to as “juniper berries,” are traditionally used as flavoring agents in food and beverages (Bais et al., 2014) Beyond culinary uses, *J. communis* has a long history in folk medicine, where berries, needles, and cones have been employed as diuretics and remedies for respiratory, digestive, and gynecological disorders (Vasilijević et al., 2018). Modern pharmacological studies have confirmed a wide range of biological activities, including antimicrobial, antioxidant, anti-inflammatory, hepatoprotective, nephroprotective, antidiabetic, and anticancer effects (Bais et al., 2014; Vasilijević et al., 2018). Chemical analyses of its essential oil and volatile fractions have identified over 20 bioactive terpenoids, with evidence of antimycobacterial and cytotoxic activities, thus supporting its traditional applications and highlighting its potential as a source of therapeutic agents (Gordien et al., 2009).

Methods

Plant Material

The essential oils of *Pogostemon cablin* (Blanco) Benth. (Patchouli) leaf and *Juniperus communis* L. (Juniper) berry were sourced from Elantra Pharmaceuticals Health Cosmetics Ltd. Sti. Phytoil Aromatherapy brand. The scientific names of the plant species used in this study were verified using the Plants of the World Online (POWO) database (https://powo.science.kew.org/). Accordingly, *Pogostemon cablin* (Blanco) Benth. and *Juniperus communis* L. were confirmed as current and accepted taxonomic names.

GC-MS and GC-FID Conditions

An Agilent system at the Eastern Anatolia High Technology Application and Research Centre (DAYTAM) was used to evaluate the oil by GC/FID and GC/MS. GC-MS analysis was performed using a Shimadzu QP2010 Ultra GC-MS system equipped with an HP-5 MS column; 30 m length x 0.25 mm ID diameter, 0.25 µm film thickness. The GC analysis included an AOC-20i autoinjector, a mass spectrometry detector and an AOC-20s sampler. The essential oils' components were identified by comparing their mass spectra with the W9N11, FFNSC library and validated by comparing the retention durations with authentic samples (Polat Sağsöz et al., 2025).

Antimicrobial Activity Assay

The antibacterial activities of the essential oil of *P. cablin* and *J. communis* against *Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 700603, *Pseudomonas aeruginosa* ATCC 27853, *Proteus mirabilis* ATCC 25933 standard bacterial strains were studied by the Kirby–Bauer diffusion method according to the guidelines of the Clinical and

Laboratory Standards Institute (CLSI) (CLSI, 2017).

Ciprofloxacin 5 µg (Bioanalyse, Türkiye), imipenem 10 µg (Bioanalyse, Türkiye) and ampicilline 10 µg (Bioanalyse, Türkiye) were used as the standard antibiotics. Essential oils were absorbed into empty and sterile antibiotic discs (10 µL for each disc). 0.5 McFarland turbidity from all bacteria for disc diffusion test suspensions was prepared and cultivated on Mueller–Hinton agar. Essential oil-impregnated discs and antibiotic discs were placed on the surface of the medium. After an overnight incubation at 37°C, the diameters of the zones formed around the discs were measured. The tests were repeated 3 times, and the averages of the zone diameters were calculated.

Drug-Likeness and Absorption-Distribution-Metabolism-Excretion-Toxicity (ADMET)

The determination of drug-likeness and ADMET profiles is crucial in structure-based drug design studies to minimize the potential side effects of promising drug candidates on the target organism. In this study, the SwissADME platform (SwissADME, 2025) was employed to predict these properties for the main bioactive compounds present in *Pogostemon cablin* (patchouli) leaf and *Juniperus communis* berry essential oils, while toxicity assessments were conducted using the ProTox-3.0 online server (Protox3, 2025). Canonical SMILES codes of the investigated compounds were obtained from the PubChem database (PubChem, 2025).

Results

GC–MS Analysis

The GC–MS analysis of *Pogostemon cablin* (Patchouli) leaf essential oil revealed that the major volatile compound was 3-Allyl-6-methoxyphenol (Chavibetol, m-Eugenol), representing 60.72% of the total composition. Other notable constituents included caryophyllene (5.47%), linalool (3.85%), eugenyl acetate (3.38%), 1-phellandrene (1.58%), α-pinene (1.57%), p-cymene (1.56%), safrole (1.71%), β-phellandrene (1.26%), and 3-phenyl-2-propenal (1.12%), a comprehensive content analysis of which is presented in Table 1.

Table 1.
Chemical composition (%) of the essential oil of P. cablin, confirmed by GC-MS

Peak#	R.Time	Area%	Name
1	3.345	0.01	Toluene
2	3.731	0.00	Hexanal
3	5.597	0.03	Styrene
4	6.454	0.01	3-methylapopinene
5	6.557	0.20	α-Thujene
6	6.782	1.57	α-Pinene
7	7.237	0.54	2,2-Dimethyl-5-methylene norbornane
8	7.532	0.35	Benzaldehyde
9	8.123	0.54	β-Pinene
10	8.527	0.18	Myrcene
11	8.911	0.01	Octanal
12	9.034	1.58	1-phellandrene
13	9.248	0.14	δ-3-carene
14	9.466	0.19	α-Terpinene
15	9.650	0.03	p-Cymenene
16	9.753	1.56	p-Cymene
17	9.932	1.26	β-Phellandrene
18	10.018	0.34	Eucalyptol
19	10.214	0.02	α- Pinene
20	10.619	0.04	β-Ocimene
21	11.062	0.03	γ-terpinene
22	11.594	0.03	Linalool oxide
23	12.155	0.02	α-terpinolene
24	12.253	0.19	2-carene
25	12.715	3.85	Linalol
26	12.866	0.09	Iso amyl iso valerate
27	13.609	0.02	p-Menth-2-en-1-ol <cis->
28	14.365	0.02	p-Menth-2-en-1-ol
29	14.604	0.02	(+)-2-bornanone
30	15.319	0.06	Benzenepropanal
31	15.408	0.08	Acetic acid, phenylmethyl ester
32	15.516	0.08	Borneol
33	16.014	0.17	Terpinene-4-ol
34	16.318	0.05	Cuminyl acetate
35	16.583	0.51	α-terpineol
36	17.064	0.05	A-phellandrene epoxide
37	18.264	0.12	Benzenepropanol
38	19.323	0.13	Chavicol
39	19.433	0.04	Acetic acid, 2-phenylethyl ester
40	20.019	1.12	2-Propenal, 3-phenyl-
41	20.090	0.78	2-Propenal, 3-phenyl-
42	20.857	1.71	Safrole
43	21.418	0.04	Carvotanacetone
44	21.715	0.12	2-Propen-1-ol, 3-phenyl-
45	24.329	60.72	Chavibetol (3-Allyl-6-methoxyphenol)
46	24.514	0.34	Benzenepropanol, acetate
47	24.749	1.34	Copaene
48	25.125	0.03	Benzyl isovalerate
49	25.385	0.03	β-Elemene
50	25.539	0.02	Vanillin
51	25.820	0.04	Isoeugenol methyl ether
52	25.990	0.02	cis-Caryophyllene
53	26.560	5.47	Caryophyllene
54	27.304	0.10	Aromadendrene
55	27.464	2.14	Cinnamyl acetate <(E)->
56	27.903	1.09	α-Humulene
57	28.808	0.03	γ-Cadinene
58	29.202	0.03	Phenethyl-2-methyl butyrate
59	29.570	0.19	(+)-Ledene
60	29.763	0.04	α-muurolene
61	30.810	3.38	Eugenol acetate
62	32.789	0.12	Spatulenol
63	33.013	0.93	Caryophyllene oxide
64	33.341	0.04	Veridiflorol
65	33.600	0.02	Humulene
66	33.703	0.05	Methoxyeugenol
67	34.004	0.19	9-eicosyne
68	34.712	0.04	Epicubenol
69	34.860	0.02	1-Oxaspiro[2.5]octane, 5,5-dimethyl-4-(3-methyl-1,3-butadienyl)-
70	34.994	0.06	Caryophylla-4(12),8(13)-dien-5-beta-ol
71	35.207	0.04	T-muurolol
72	35.662	0.03	Cadin-4-en-10-ol
73	35.779	0.04	3-methyl-5-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1-pentyn-3-ol
74	36.269	0.07	Viridiflorol
75	38.384	0.04	4-Hydroxy-2-methoxycinnamaldehyde

76	38.551	0.08	Coniferyl alcohol <(Z)->
77	39.626	0.07	Benzyl benzoate
78	42.290	0.03	2-Pentadecanone, 6,10,14-trimethyl-
79	42.623	0.05	Benzoate <phenethyl->
80	50.761	0.02	Thymoquinone
81	51.095	0.02	1H-Indole, 2-(1,1-dimethyl-2-propenyl)-6-(3-methyl-2-butenyl)-
82	51.842	0.02	2-tripropylsilyloxynaphthene
83	60.697	0.02	9,12-Octadecadienoic acid (Z,Z)-
84	61.750	0.02	Benzene, 1-methoxy-4-(2-propenyl)-
85	62.484	0.05	Dehydrodiisoeugenol

The GC–MS analysis of *Juniperus communis* berry essential oil identified methyl salicylate as the predominant constituent, accounting for 80.86% of the total composition. Other major components included (-)-terpinen-4-ol (4.23%), p-cymene (2.60%), trielaidin (2.26%), and Linoleoyl chloride (2.08%). Minor compounds detected were carvone (0.69%), limonene (0.60%), 1,8-cineole (0.60%), α-terpineol (0.42%), and (+)-2-bornanone (0.42%), a comprehensive content analysis of which is presented in Table 2.

Table 2.
Chemical composition (%) of the essential oil of J. communis, confirmed by GC-MS

Peak#	R.Time	Area%	Name
1	3.735	0.12	Hexanal <n->
2	6.559	0.06	α-thujene
3	6.782	1.15	α-Pinene
4	7.032	0.08	Hydroperoxide, 1-ethylbutyl
5	7.239	0.11	Camphene
6	7.326	0.10	2-Pentanol, 4-methyl-
7	8.137	0.10	2-β-pinene
8	8.522	0.16	Heptane, 2,2,4,6,6-pentamethyl-
9	9.246	0.33	δ-3-carene
10	9.745	2.60	p-Cymene
11	9.910	0.60	Limonene
12	10.015	0.60	1,8-cineole
13	11.059	0.28	γ-terpinene
14	12.258	0.10	2-carene
15	12.672	0.15	Linalyl anthranilate
16	14.602	0.42	(+)-2-bornanone
17	15.139	0.23	Isoborneol
18	16.016	4.23	3-Cyclohexen-1-ol,4-methyl-1-(1-methylethyl)-, (R)-
19	16.609	0.42	α-terpineol
20	16.825	80.86	Methyl salicylate
21	17.000	0.14	6-(Aminomethyl)cyclohex-2-enemethanol
22	18.883	0.69	Carvone
23	19.320	0.21	4-Nonanone, 7-ethyl-
24	21.048	0.30	2,4-decadienal, (e,e)-
25	21.347	0.23	Limonene dioxide 1
26	21.510	0.11	p-Menthane
27	22.011	0.40	Deca-(2E,4E)-dienal
28	26.468	0.17	Trans-β-caryophyllene
29	32.986	0.12	Caryophyllene oxide
30	56.046	0.26	1,3-Propanediol dipalmitate
31	59.454	0.09	9,12-Octadecadienoic acid (Z,Z)-, 2,3-dihydroxypropyl ester
32	60.686	2.08	Linoleoyl chloride
33	60.812	2.26	Trielaidin
34	61.045	0.24	Adipic acid, cis-non-3-enyl isobutyl ester

Antibacterial Activity

The antibacterial activity results, as presented in Table 3, demonstrated that P. cablin leaf oil exhibited moderate inhibition against Staphylococcus aureus with a zone diameter of 36 mm, while it showed no activity against Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, and Pseudomonas aeruginosa. Similarly, J. communis berry oil was effective only against S. aureus with an inhibition zone of greater than 40 mm, but it was inactive against the other tested bacteria. In contrast, the reference antibiotics showed broader antibacterial activity. Ciprofloxacin produced inhibition zones ranging from 30 mm to 46 mm against all tested strains, with the highest activity observed against P. aeruginosa (46 mm). Imipenem demonstrated strong effects, particularly against S. aureus (50 mm), while ampicillin displayed limited effectiveness, with only moderate inhibition against S. aureus (25 mm) and P. aeruginosa (27 mm), and no effect on K. pneumoniae or P. mirabilis. These findings suggest that while the tested essential oils have selective antibacterial potential, particularly against S. aureus, standard antibiotics remain more effective across a wider range of pathogens.

Table 3.
Antibacterial activity of P. cablin leaf oil, J. communis berry oil, and standard antibiotics against selected pathogenic bacteria (inhibition zone diameters, mm)

No	*S. aureus*	*E. coli*	*K. pneumoniae*	*P. mirabilis*	*P. aeruginosa*
P. cablin Leaf Oil	36	R*	R	R	R
J. communis Berry Oil	>40	R	R	R	R
Ciprofloxacin	30	43	30	35	46
Imipenem	50	36	35	25	25
Ampicillin	25	10	R	R	27

*R: Resistance

ADMET Properties of The Major Constituents

ADMET analyses were performed for the major constituents of *Juniperus communis* essential oil, namely methyl salicylate, (−)-terpinen-4-ol, and p-cymene, and their absorption, distribution, metabolism, excretion, and drug-likeness profiles were evaluated. As shown in Table 4 and Figure 1, the pharmacokinetic profiles of these three compounds exhibit distinct advantages and limitations for both oral and topical applications.

Figure 1.
Radar plots representing the drug-likeness parameters (lipophilicity, size, polarity, solubility, flexibility, and unsaturation) of the major constituents of Juniperus communis essential oil: methyl salicylate, (−)-terpinen-4-ol, and p-cymene

Methyl salicylate **(-)-Terpinen-4-ol** **p-Cymene**

Table 4.

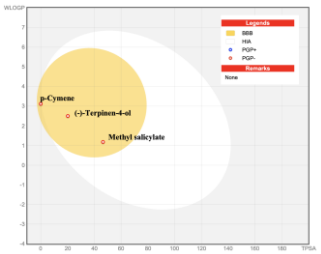
Structural, physicochemical, and ADMET properties of the major constituents of Juniperus communis essential oil: methyl salicylate, (−)-terpinen-4-ol, and p-cymene

Property	Methyl salicylate	(-)-Terpinen-4-ol	p-Cymene
Molecular weight	152.15 g/mol	154.25 g/mol	134.22 g/mol
Num. heavy atoms	11	11	10
Num. arom. heavy atoms	6	0	6
Fraction Csp3	0.12	0.80	0.40
Num. rotatable bonds	2	1	1
Num. H-bond acceptors	3	1	0
Num. H-bond donors	1	1	0
Molar Refractivity	39.74	48.80	45.99
TPSA	46.53 Å²	20.23 Å²	0.00 Å²
Log P (iLOGP)	2.03	2.51	2.51
Log P (XLOGP3)	2.55	3.26	4.10
Log P (WLOGP)	1.18	2.50	3.12
Log P (MLOGP)	1.32	2.30	4.47
Log P (SILICOS-IT)	1.21	2.44	3.29
Consensus Log P	1.66	2.60	3.50
Log S (ESOL)	-2.66	-2.78	-3.63
Solubility (ESOL)	3.32e-01 mg/ml; 2.18e-03 mol/l	2.54e-01 mg/ml; 1.64e-03 mol/l	3.12e-02 mg/ml; 2.33e-04 mol/l
Class (ESOL)	Soluble	Soluble	Soluble
Log S (Ali)	-3.17	-3.36	-3.81
Log S (SILICOS-IT)	-1.88	-1.91	-3.57
Class (Ali)	Soluble	Soluble	Soluble
Solubility (Ali)	1.02e-01 mg/ml; 6.69e-04 mol/l	6.75e-02 mg/ml; 4.38e-04 mol/l	2.10e-02 mg/ml; 1.56e-04 mol/l
Solubility (SILICOS-IT)	2.00e+00 mg/ml; 1.32e-02 mol/l	1.92e+00 mg/ml; 1.24e-02 mol/l	3.58e-02 mg/ml; 2.67e-04 mol/l
Class (SILICOS-IT)	Soluble	Soluble	Soluble
GI absorption	High	High	Low
BBB permeant	Yes	Yes	Yes
P-gp substrate	No	No	Yes
CYP1A2 inhibitor	No	No	No
CYP2C19 inhibitor	No	No	No
CYP2C9 inhibitor	No	No	No
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	No	No	No
Log Kp (skin permeation)	-5.42 cm/s	-4.93 cm/s	-4.21 cm/s
Lipinski	Yes; 0 violation	Yes; 0 violation	Yes; 1 violation: MLOGP>4.15
Ghose	No; 3 violations: MW<160, MR<40, #atoms<20	No; 1 violation: MW<160	No; 1 violation: MW<160
Veber	Yes	Yes	Yes
Egan	Yes	Yes	Yes
Muegge	No; 1 violation: MW<200	No; 2 violations: MW<200, Heteroatoms<2	No; 2 violations: MW<200, Heteroatoms<2
Bioavailability Score	0.55	0.55	0.55
PAINS	0 alert	0 alert	0 alert
Brenk	0 alert	1 alert: isolated_alkene	0 alert
Leadlikeness	No; 1 violation: MW<250	No; 1 violation: MW<250	No; 2 violations: MW<250, XLOGP3>3.5
Synthetic accessibility	1.11	3.28	1.00

The Boiled-Egg model is a simple yet effective predictive tool that visualizes the pharmacokinetic behavior of small molecules in terms of gastrointestinal absorption (HIA), blood–brain barrier (BBB) permeability, and P-gp substrate status, as shown in Figure 2 for the major constituents of *J. communis* essential oil, namely methyl salicylate, (−)-terpinen-4-ol, and *p*-cymene.

Figure 2.

Boiled-Egg model results of the major constituents of Juniperus communis essential oil: methyl salicylate, (−)-terpinen-4-ol, and p-cymene.



Predicted Toxicity Profiles of Major Constituents

Based on the ProTox-3.0 predictions, methyl salicylate exhibited a moderate level of toxicity with an estimated oral LD_{50} value of 887 mg/kg and classification in toxicity class 4. The compound was predicted to be active for hepatotoxicity and nephrotoxicity, suggesting a potential risk for liver and kidney impairment at elevated doses, while no significant risks were indicated for neurotoxicity, cardiotoxicity, or respiratory toxicity (Table 5).

Table 5.

Summary of protox-3.0 predicted toxicological profiles of methyl salicylate, (−)-terpinen-4-ol, and p-cymene

Molecule	LD_{50} (mg/kg)	Toxicity Class	Key Organ Toxicities	BBB Penetration	Carcinogenicity / Mutagenicity	Notable Metabolism Interaction
Methyl salicylate	887	4	Hepatotoxicity (active), Nephrotoxicity (active)	Active (0.85)	Inactive	CYP2C9 (active)
(-)-Terpinen-4-ol	1016	4	Not calculated	Not calculated	Not calculated	Not calculated
***p*-Cymene**	3	1	Respiratory toxicity (active)	Active (0.99)	Inactive	CYP2C9 (active)

ADMET Properties of The Major Constituents of *P. cablin*

ADMET analyses were performed for the major constituents of *Pogostemon cablin* essential oil, namely linalool, caryophyllene, and chavibetol, and their absorption, distribution, metabolism, excretion, and drug-likeness profiles were evaluated. As shown in Table 6 and Figure 3, the pharmacokinetic profiles of these three compounds demonstrate distinct advantages and limitations for both oral and topical applications.

Figure 3.

Radar plots representing the drug-likeness parameters (lipophilicity, size, polarity, solubility, flexibility, and unsaturation) of the major constituents of Pogostemon cablin essential oil: linalool, caryophyllene, and chavibetol

Linalool **Caryophyllene** **Chavibetol**

Table 6.

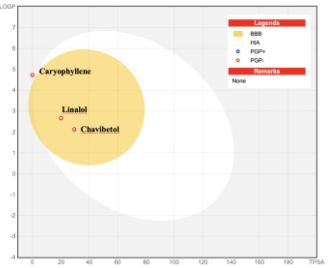
Structural, physicochemical, and ADMET properties of the major constituents of Pogostemon cablin essential oil: linalool, caryophyllene, and chavibetol

Category	Linalool	Caryophyllene	Chavibetol
Formula	$C_{10}H_{18}O$	$C_{15}H_{24}$	$C_{10}H_{12}O_2$
Molecular weight	154.25 g/mol	204.35 g/mol	164.20 g/mol
Num. heavy atoms	11	15	12
Num. arom. heavy atoms	0	0	6
Fraction Csp3	0.60	0.73	0.20
Num. rotatable bonds	4	0	3
Num. H-bond acceptors	1	0	2
Num. H-bond donors	1	0	1
Molar Refractivity	50.44	68.78	49.06
TPSA	20.23 Å²	0.00 Å²	29.46 Å²
Log P (iLOGP)	2.70	3.25	2.34
Log P (XLOGP3)	2.97	4.38	2.27
Log P (WLOGP)	2.67	4.73	2.13
Log P (MLOGP)	2.59	4.63	2.01
Log P (SILICOS-IT)	2.35	4.19	2.48
Consensus Log P	2.66	4.24	2.25
Log S (ESOL)	-2.40	-3.87	-2.46
Solubility (ESOL)	6.09e-01 mg/ml; 3.95e-03 mol/l	2.78e-02 mg/ml; 1.36e-04 mol/l	5.69e-01 mg/ml; 3.47e-03 mol/l
Class (ESOL)	Soluble	Soluble	Soluble
Log S (Ali)	-3.06	-4.10	-2.53
Solubility (Ali)	1.35e-01 mg/ml; 8.75e-04 mol/l	1.64e-02 mg/ml; 8.01e-05 mol/l	4.90e-01 mg/ml; 2.98e-03 mol/l
Class (Ali)	Soluble	Moderately soluble	Soluble
Log S (SILICOS-IT)	-1.84	-3.77	-2.79
Solubility (SILICOS-IT)	2.20e+00 mg/ml; 1.43e-02 mol/l	3.49e-02 mg/ml; 1.71e-04 mol/l	2.65e-01 mg/ml; 1.61e-03 mol/l
Class (SILICOS-IT)	Soluble	Soluble	Soluble
GI absorption	High	Low	High
BBB permeant	Yes	No	Yes
P-gp substrate	No	No	No
CYP1A2 inhibitor	No	No	No
CYP2C19 inhibitor	No	Yes	No
CYP2C9 inhibitor	No	Yes	No
CYP2D6 inhibitor	No	Yes	No
CYP3A4 inhibitor	No	No	No
Log Kp (skin permeation)	-5.13 cm/s	-4.44 cm/s	-5.69 cm/s
Lipinski	Yes; 0 violation	Yes; 1 violation: MLOGP>4.15	Yes; 0 violation
Ghose	No; 1 violation: MW<160	Yes	Yes
Veber	Yes	Yes	Yes
Egan	Yes	Yes	Yes
Muegge	No; 2 violations: MW<200, Heteroatoms<2	No; 1 violation: Heteroatoms<2	No; 1 violation: MW<200
Bioavailability Score	0.55	0.55	0.55
PAINS	0 alert	0 alert	0 alert
Brenk	1 alert: isolated_alkene	1 alert: isolated_alkene	1 alert: isolated_alkene
Leadlikeness	No; 1 violation: MW<250	No; 2 violations: MW<250, XLOGP3>3.5	No; 1 violation: MW<250
Synthetic accessibility	2.74	4.51	1.51

The Boiled-Egg model is a simple yet effective predictive tool that visualizes the pharmacokinetic behavior of small molecules in terms of gastrointestinal absorption (HIA), blood–brain barrier (BBB) permeability, and P-gp substrate status, as shown in Figure 4 for the major constituents of *P. cablin* essential oil, namely linalool, caryophyllene, and chavibetol.

Figure 4.

Boiled-Egg model results of the major constituents of Pogostemon cablin essential oil: linalool, caryophyllene, and chavibetol



Predicted Toxicity Profiles of Major Constituents of *Pogostemon cablin*

Based on the ProTox-3.0 predictions, chavibetol shows a generally favorable acute toxicity profile, although the LD_{50} value and overall toxicity class were not reported in the provided export. Among organ-toxicity models, neurotoxicity was flagged active (probability ≈0.50), whereas hepatotoxicity, nephrotoxicity, cardiotoxicity, and respiratory toxicity were predicted inactive (Table 7).

Table 7.
Summary of protox-3.0 predicted toxicological profiles of linalool, caryophyllene, and chavibetol (major constituents of Pogostemon cablin essential oil)

Molecule	LD50 (mg/kg)	Toxicity Class	Key Organ Toxicities	BBB Penetration	Carcinogenicity / Mutagenicity	Notable Metabolism Interaction
Linalool	2200	5	Hepato, Neuro, Nephro, Respiratory, Cardio: Inactive	Active (0.92)	Inactive / Inactive	CYP2C9 (active); CYP1A2 / 2C19/ 2D6/ 3A4/ 2E1 inactive
Caryophyllene	5300	5	Immunotoxicity (active 0.54); others inactive	Active (0.97)	Inactive / Inactive	CYP1A2 / 2C19/ 2D6/ 3A4/ 2E1 inactive
Chavibetol	—	—	Not available from uploaded file	—	—	—

Discussion

In the essential oil of *Pogostemon cablin* leaves, the predominant compound was identified as 3-allyl-6-methoxyphenol (chavibetol, 60.72%), whereas in the study by Silva-Filho et al. (2016), the major constituents were reported as patchoulol (38.5%), α-bulnesene (20.37%), α-guaiene (12.31%), seychellene (8.33%), and α-patchoulene (4.91%). This discrepancy may be attributed to various factors such as the geographical origin of the plant, climatic conditions, harvest time, extraction methods, and analytical procedures employed

The variation in the volatile oil composition of *P. cablin* is mainly influenced by genetic, environmental, and methodological factors. The presence of distinct chemotypes such as pogostone-type and patchouliol-type reflects genetic diversity that affects terpenoid biosynthesis (Hu et al., 2006; Luo et al., 2003). Environmental parameters—such as soil type, temperature, humidity, altitude, and light intensity—further modulate secondary metabolite production. Seasonal changes, harvest time, and geographical origin also contribute to differences in essential oil yield and composition, as reported in samples from China, Vietnam, Indonesia, and the Philippines (Buré & Sellier, 2004; Dung et al., 1990; Hasegawa et al., 1992; Luo et al., 1999). Moreover, extraction and analytical methods play a crucial role; conventional distillation may cause thermal degradation of certain compounds, while advanced techniques like supercritical CO_2 or microwave-assisted extraction provide higher-quality oils (Donelian et al., 2009; Masrur, 2008) Therefore, the chemical diversity of *P. cablin* essential oils arises from the combined effects of genetic variation and external environmental and technical conditions. (Silva-Filho et al., 2016; Swamy & Sinniah, 2015).

According to the ADTU (2025) review, sesquiterpenes such as patchouli alcohol and pogostone have been highlighted as the primary bioactive compounds, known for their anti-inflammatory, antioxidant, antimicrobial, and anticancer activities (Khaidem et al., 2025).

The essential oil from berries of *Juniperus communis* L. subsp. *alpina*, a total of 65 compounds were identified, accounting for 95.3% of the oil, with monoterpene hydrocarbons (82.0%) being the predominant class, particularly limonene (49.3%) and α-pinene (22.1%), while sesquiterpenes such as germacrene-D (2.0%), δ-cadinene (1.2%), and β-elemene (1.1%), together with oxygenated monoterpenes represented mainly by α-terpinyl acetate (5.3%), were reported as the major secondary constituents (Gonny et al., 2006).

According to antimicrobial activity result, *P. cablin* and *J. communis* essential oils antimicrobial activities of on Gram-positive bacteria are higher than on Gram-negative bacteria. This suggests that the targets of essential oils are more intensely expressed in Gram-positive bacteria. However, further studies are needed to confirm this idea (Dechayont et al., 2017; Galovičová et al., 2022; Mërtiri et al., 2024).

In a previous study, *Juniperus communis* essential oil showed strong antibacterial activity at 1–5 mg/L. The highest sensitivity was observed in *E. coli* (25–39 mm) and *S. aureus* (16–29 mm), while *Hafnia alvei* showed weak inhibition (9–13 mm) and *P. aeruginosa* remained resistant (Haziri et al., 2013). The GC–MS results of the present study indicated that *J. communis* essential oil was mainly composed of methyl salicylate, (–)-terpinen-4-ol, and p-cymene, all of which demonstrated strong antibacterial potential against *S. aureus.* These findings partially differ from previous reports on *J. communis* oils obtained from different geographical origins. For instance, juniper berry oil from Bulgaria was reported to be dominated by monoterpene hydrocarbons such as α-pinene (51.4%), myrcene (8.3%), sabinene (5.8%), limonene (5.1%), and β-pinene (5.0%) (Höferl et al., 2014). Similarly, (Maurya et al., 2018) observed that the essential oils of *J. communis* and its wild relatives contained α-pinene, limonene, and sabinene as major constituents, and displayed stronger antibacterial effects against Gram-positive bacteria (*S. aureus*) than Gram-negative ones, consistent with our results. However, in the present study, the predominance of oxygenated monoterpenes such as (–)-terpinen-4-ol and p-cymene instead of hydrocarbon monoterpenes indicates a potential chemotypic variation that might be attributed to ecological conditions or extraction parameters. The observed differences in composition

are also reflected in the biological activities; while α-pinene-rich oils have been mostly associated with antioxidant effects, the higher proportion of (–)-terpinen-4-ol in our sample may account for its more pronounced antibacterial activity. Therefore, the compositional and bioactivity variations among *J. communis* essential oils reported in the literature highlight the importance of geographical origin, genetic diversity, and chemotype characterization in assessing their pharmacological potential.

P. cablin essential oil exhibited limited antibacterial effects, with the lowest inhibition zones recorded for *Pseudomonas aeruginosa* (1 mm) and *Salmonella enterica* (1.67 mm). Moderate activity was observed against Gram-positive bacteria such as *Staphylococcus aureus* (4.33 mm) and *Enterococcus faecalis* (5.67 mm), while the strongest effects were noted against yeasts, particularly *Candida krusei* (19 mm), *C. albicans* (16 mm), and *C. tropicalis* (17.67 mm) (Galovičová et al., 2022). Our present study is partially consistent with the findings of previous studies and also highlights important chemotypic differences between *P. cablin* oils from different sources. For instance, a study on the Indian high-yielding variety CIM-Utkrisht reported sesquiterpenoid-rich oils, especially γ-curcumene (22–25%), ar-curcumene (1.3–3.1%), and bisabolane-type sesquiterpenoids, with marked anti-inflammatory (TNF-α reduction, $p< 0.05$) and antimicrobial activities against *Candida albicans, S. typhimurium,* and *S. aureus* (Srivastava et al., 2022). In contrast, another comparative investigation demonstrated that patchouli leaf and flower oils were dominated by patchouli alcohol (27.52–44.52%) and caryophyllene (12.86–18.23%), exhibiting variable biological properties such as antioxidant, anti-diabetic, and anti-inflammatory activities (Pandey et al., 2022).

S. aureus is an important pathogen that can cause a wide variety of infections, from mild skin and soft tissue infections such as abscesses and boils to very serious infections such as bloodstream, bone and joint infections. The most important problem with this bacterium is that it can easily acquire antimicrobial resistance through mutation or horizontal transfer of resistance genes from other bacteria (Linz et al., 2023; Pinho Mariana et al., 2025).

Although these findings provide insight into the antimicrobial activities of *P. cablin* and *J. communis* essential oils, in order to more clearly demonstrate the antimicrobial activities of these essential oils, it would be appropriate to conduct further studies using more bacterial species and to determine minimum inhibitory concentration values. This situation constitutes a limitation of our study.

According to ADMET results, Methyl salicylate exhibits high gastrointestinal absorption, moderate lipophilicity (Consensus LogP 1.66), and good aqueous solubility, supporting a favorable oral bioavailability profile. The absence of P-gp substrate status reduces the risk of active efflux at the intestinal and blood–brain barrier levels. Its TPSA value (46.53 Å²) is suitable for passive membrane permeability, while dermal penetration is moderate/low (log Kp −5.42 cm/s). It does not inhibit major CYP isoenzymes, minimizing the risk of drug–drug interactions. Due to its ester structure, it is expected to undergo hydrolysis by esterases to form salicylates *in vivo*. No Lipinski violations are detected, and the bioavailability score is 0.55. These features make it advantageous for CNS-targeted applications, although topical absorption remains limited.

(−)-Terpinen-4-ol demonstrates high gastrointestinal absorption (Consensus LogP 2.60), low TPSA (20.23 Å²), and a favorable solubility profile, making it suitable for both oral and dermal applications. Its non-substrate status for P-gp provides an additional advantage for absorption and distribution. Dermal penetration (log Kp −4.93 cm/s) is higher than that of methyl salicylate. It does not inhibit major CYP isoenzymes; however, the Brenk filter indicates one alert (isolated alkene), suggesting potential oxidative metabolite formation. With no Lipinski violations and a bioavailability score of 0.55, it appears promising for oral and topical use, although oxidative and photostability testing is recommended.

p-Cymene shows poor gastrointestinal absorption despite its high lipophilicity (Consensus LogP 3.50) and extremely low polarity (TPSA 0 Å²). Its P-gp substrate status may further limit absorption and BBB penetration. Although classified as “soluble” in predictive models, its practical solubility is relatively low. Among the three compounds, p-cymene demonstrates the highest dermal penetration (log Kp −4.21 cm/s), making it favorable for transdermal and dermal formulations. It does not inhibit major CYP isoenzymes, but its high lipophilicity suggests predominant phase-I oxidation followed by phase-II conjugation metabolism. Lipinski analysis indicates one violation (MLOGP > 4.15), classifying it as marginally drug-like. Oral bioavailability is poor but may be improved using lipid-based carriers or nanoemulsions. Its strong dermal penetration highlights its potential for topical and inhalation applications.

Analysis of the major constituents of *J. communis* essential oil showed that all three compounds fall within the BBB area. p-Cymene, with its zero TPSA and high lipophilicity, is highly permeable across the BBB; however, its P-gp substrate (+) status may limit its accumulation in brain tissues. (−)-Terpinen-4-ol, characterized by a moderate TPSA (~20 Å²) and balanced lipophilicity (WLOGP ~2.5), demonstrates both high gastrointestinal absorption and effective BBB penetration. Importantly, its non-substrate (−) status for P-gp enhances passive diffusion into the central nervous system, making it the most balanced candidate in terms of oral bioavailability and CNS accessibility. Methyl salicylate, despite having a slightly higher TPSA (~46 Å²) and lower lipophilicity, still shows BBB permeability. Its non-substrate (−) status for P-gp confers an additional advantage for central effects, while its high gastrointestinal absorption supports a versatile pharmacokinetic profile. Overall, all three compounds are likely to exhibit central effects, with (−)-terpinen-4-ol standing out as the most favorable in terms of combined oral bioavailability and BBB permeability.

Importantly, methyl salicylate showed the ability to cross the blood–brain barrier, which may account for possible central nervous system effects, and a low probability of clinical toxicity was also reported. On the other hand, carcinogenicity, mutagenicity, cytotoxicity, and immunotoxicity endpoints were predicted as inactive, highlighting a low risk for genotoxic or cancer-related effects. Molecular initiating event analysis

indicated potential interactions with transthyretin (TTR) and GABA receptors, which may contribute to neurological responses, whereas metabolic profiling revealed a possible interaction with CYP2C9, suggesting drug–drug interaction risks. Overall, methyl salicylate appears to be moderately toxic with organ-specific liabilities but limited evidence of long-term genotoxic hazards (Table 5).

According to the ProTox-3.0 prediction results, (−)-terpinen-4-ol was estimated to have an oral LD_{50} value of 1016 mg/kg, placing it in toxicity class 4, which indicates a moderate level of toxicity. While specific organ toxicity, endpoint classifications, and molecular initiating event predictions were still under calculation in the report, the available data suggest that the compound does not exhibit acute high toxicity and has a relatively safe profile at lower doses. The physicochemical properties, including a LogP value of 2.5 and a low topological polar surface area (20.23 Å²), indicate good membrane permeability and potential for systemic absorption. In terms of toxicity targets, possible weak binding affinity was observed for the androgen receptor, although the overall pharmacophore fit remained low, suggesting limited relevance. Taken together, (−)-terpinen-4-ol appears to be moderately toxic at higher concentrations but may be considered relatively safe at therapeutic levels, warranting further evaluation in experimental toxicity studies to clarify its organ-specific effects (Table 5).

According to the ProTox-3.0 predictions, *p*-cymene demonstrated a very high level of predicted toxicity, with an estimated oral LD_{50} value of only 3 mg/kg and classification in toxicity class 1, which indicates extreme toxicity. Most organ toxicity endpoints, including hepatotoxicity, nephrotoxicity, neurotoxicity, and cardiotoxicity, were predicted to be inactive; however, respiratory toxicity was flagged as active with moderate probability. Importantly, the compound showed strong potential to cross the blood–brain barrier (0.99), raising concerns for central nervous system exposure, and was also predicted to display ecotoxic effects. Carcinogenicity, mutagenicity, immunotoxicity, and cytotoxicity were predicted as inactive, suggesting low risk of genotoxic or long-term carcinogenic hazards. Additionally, CYP2C9 interaction was predicted as active, indicating a possibility of drug–drug interactions at the metabolic level. Overall, *p*-cymene is characterized by an extremely low LD_{50} and high predicted toxicity, highlighting the need for careful handling and further experimental studies to validate its safety profile (Table 5).

p-Cymene, a monocyclic monoterpene hydrocarbon commonly used as a flavoring agent, was evaluated for its subchronic toxicity in rats over 90 days at doses of 0, 2.4, 12, and 60 mg/kg/day. No mortality or significant clinical abnormalities were observed. However, at 60 mg/kg, changes in hematological, biochemical, and urinary parameters, as well as increased liver weight and hepatocellular hypertrophy, were detected. Therefore, the no-observed-adverse-effect level (NOAEL) for p-cymene was determined to be 12 mg/kg/day for both sexes (Kuwagata et al., 2024).

Linalool demonstrated favorable drug-likeness with high gastrointestinal absorption and blood–brain barrier (BBB) permeability. Its moderate lipophilicity (Consensus LogP 2.66) and low TPSA (20.23 Å²) support good membrane permeability. Solubility predictions classified it as “soluble” across multiple models, which aligns with its potential for oral bioavailability. The absence of P-gp substrate status and lack of CYP inhibition indicate a low risk of efflux or drug–drug interactions. Dermal penetration (log Kp −5.13 cm/s) is moderate, suggesting balanced absorption for both oral and topical routes. With no Lipinski violations and a bioavailability score of 0.55, linalool can be considered a promising candidate for systemic as well as dermal formulations, although its isolated alkene alert points to the need for oxidative stability assessment.

Caryophyllene displayed comparatively higher lipophilicity (Consensus LogP 4.24) and lower polarity (TPSA 0 Å²), consistent with low gastrointestinal absorption and lack of BBB permeability. Although classified as moderately soluble or soluble depending on the model, its poor oral absorption limits its systemic bioavailability. Its dermal penetration rate (log Kp −4.44 cm/s) is relatively high, favoring topical application. Importantly, caryophyllene was predicted to inhibit multiple CYP isoenzymes (CYP2C19, CYP2C9, CYP2D6), which could pose significant risks for metabolic drug–drug interactions. One Lipinski violation (MLOGP > 4.15) and a lower synthetic accessibility score further constrain its drug-likeness. Overall, caryophyllene appears more suited for dermal formulations, although its metabolic liabilities warrant careful evaluation.

Chavibetol exhibited high gastrointestinal absorption and BBB permeability, supported by its moderate lipophilicity (Consensus LogP 2.25) and TPSA of 29.46 Å². Solubility was consistently predicted as good across models, highlighting favorable oral and dermal bioavailability. Dermal penetration (log Kp −5.69 cm/s) was somewhat lower than caryophyllene but acceptable for topical delivery. Chavibetol did not inhibit major CYP isoenzymes and presented no Lipinski violations, suggesting a safer pharmacokinetic profile. Its bioavailability score of 0.55 and relatively low synthetic accessibility (1.51) emphasize its potential as a drug-like candidate. The presence of an isolated alkene alert, however, points to possible oxidative liability.

Analysis of the major constituents of *P. cablin* essential oil revealed that all three compounds fall within the BBB-permeant region of the Boiled-Egg model. Caryophyllene, characterized by its zero TPSA and high lipophilicity (WLOGP ~5), demonstrates strong BBB permeability; however, its very low polarity and excessive lipophilicity may reduce gastrointestinal absorption efficiency, limiting its systemic bioavailability. Linalool, with a moderate TPSA (~20 Å²) and balanced lipophilicity (WLOGP ~2.7), shows high gastrointestinal absorption and effective BBB penetration. Importantly, its non-substrate (−) status for P-gp supports favorable passive diffusion into the central nervous system, making it a well-balanced candidate for oral and CNS-targeted applications. Chavibetol, possessing a TPSA of ~29 Å² and moderate lipophilicity (WLOGP ~2.2), also demonstrates good gastrointestinal absorption and BBB permeability. Like linalool, its non-substrate (−) status for P-gp enhances CNS accessibility, though its phenolic structure suggests possible metabolic liabilities. Overall, all three compounds are likely to

exert central effects, with linalool representing the most favorable candidate in terms of balanced oral bioavailability and BBB penetration.

The chavibetol was predicted to cross the blood–brain barrier (BBB(+), ≈0.76), while clinical toxicity and ecotoxicity were inactive. Likewise, carcinogenicity, mutagenicity, cytotoxicity, and immunotoxicity endpoints were predicted inactive, indicating a low risk for genotoxic or cancer-related effects. At the molecular level, a potential interaction with the GABA receptor (active ≈0.65) was indicated, and metabolism modeling suggested possible interactions with CYP2C9 (active ≈0.69) and CYP2C19 (active ≈0.50), pointing to plausible drug–drug interaction liabilities. Overall, chavibetol appears to be low in acute and organ-specific toxicity but warrants caution regarding CNS exposure and CYP2C9/2C19-mediated metabolic interactions (Table 7).

Based on the ProTox-3.0 predictions, linalool exhibited low acute toxicity with an estimated oral LD_{50} of 2200 mg/kg and assignment to toxicity class 5. All screened organ-toxicity endpoints—including hepatotoxicity, nephrotoxicity, neurotoxicity, cardiotoxicity, and respiratory toxicity—were predicted inactive, and the Tox21 nuclear-receptor and stress-response panels were likewise inactive. Notably, linalool showed a high probability of crossing the blood–brain barrier (BBB(+), 0.92), while clinical toxicity was predicted inactive. Carcinogenicity, mutagenicity, cytotoxicity, and immunotoxicity were all inactive, indicating a low risk of genotoxic or cancer-related effects. Molecular initiating events were broadly negative across the panel, and metabolism modeling suggested a possible interaction with CYP2C9 (active), whereas other major CYP isoenzymes were inactive. Ecotoxicity was flagged as active with modest probability, warranting environmental caution. Overall, linalool appears to have a favorable safety profile characterized by low acute toxicity and minimal organ liabilities, with BBB permeability and potential CYP2C9-mediated interaction as considerations (Table 7).

Based on the ProTox-3.0 predictions, caryophyllene exhibited low acute toxicity, with an estimated oral LD_{50} of 5300 mg/kg and assignment to toxicity class 5. All primary organ-toxicity models (hepatotoxicity, nephrotoxicity, neurotoxicity, cardiotoxicity, and respiratory toxicity) were predicted inactive, and carcinogenicity, mutagenicity, and cytotoxicity were likewise inactive; however, immunotoxicity was flagged active with modest probability, warranting attention in follow-up studies. Notably, caryophyllene showed a high likelihood of crossing the blood–brain barrier (BBB(+), 0.97), while clinical toxicity was predicted inactive. Across the Tox21 nuclear receptor and stress-response panels, activities were broadly inactive, and molecular initiating event models were uniformly negative. Metabolism modeling indicated a potential interaction with CYP2C9 (active), whereas other major CYP isoenzymes were predicted inactive, suggesting a limited but plausible drug–drug interaction risk. Ecotoxicity was also predicted active, indicating environmental caution. Overall, caryophyllene presents a favorable safety profile in terms of acute and organ-specific toxicity, with BBB permeability, an immunotoxicity signal, and possible CYP2C9-mediated interactions as the principal considerations (Table 7).

Conclusion

Taken together, the strong anti-staphylococcal activity of Pogostemon cablin and Juniperus communis essential oils—contrasted with limited effects on Gram-negative bacteria—combined with in silico ADMET/toxicity readouts (drug-likeness and favorable GI/BBB permeability for linalool and chavibetol; acceptable liabilities for (−)-terpinen-4-ol and methyl salicylate; and a toxicity signal for p-cymene) supports their further development primarily for anti-staphylococcal applications, preferably via topical or inhalational delivery and/or formulation strategies to broaden Gram-negative coverage while mitigating p-cymene-associated risks, to be confirmed by mechanistic and in vivo studies.

Peer-review: Externally peer-reviewed.
Author Contributions: Concept – L.G.; Design – H.H.; Supervision – L.G.; Resources – L.G.; Materials – L.G., H.H.; Data Collection and/or Processing – L.G., H.H.; Analysis and/or Interpretation – L.G., H.H.; Literature Search – L.G., H.H.; Writing – L.G.; Critical Review- L.G.
Conflict of Interest: The authors have no conflicts of interest to declare.
Financial Disclosure: The authors declared that this study has received no financial support.
Use of Artificial Intelligence: The authors declared that artificial intelligence has been used solely for language and grammar correction.
Acknowledgements: We would like to thank Prof. Dr. Yavuz Bülent KÖSE for identifying the plant.

Hakem Değerlendirmesi: Dış bağımsız.
Yazar Katkıları: Konsept – L.G.; Tasarım – H.H.; Denetim – L.G.; Kaynaklar – L.G.; Materyaller – L.G., H.H.; Veri Toplanması ve/veya İşlenmesi – L.G., H.H.; Analiz ve/veya Yorumlama – L.G., H.H.; Literatür Taraması – L.G., H.H.; Yazım – L.G.; Eleştirel İnceleme- L.G.
Çıkar Çatışması: Yazarlar, çıkar çatışması olmadığını beyan etmiştir.
Finansal Destek: Yazarlar, bu çalışma için finansal destek almadığını beyan etmiştir.
Yapay Zeka Kullanımı: Yazarlar, bu çalışma için yapay zekanın yalnızca dil ve gramer düzeltmesi için kullanıldığını beyan etmiştir.
Teşekkür: Bitkiyi tanımlama konusundaki katkısından dolayı Prof. Dr. Yavuz Bülent KÖSE'ye teşekkür ederiz.

References

Bais, S., Gill, N. S., Rana, N., & Shandil, S. (2014). A Phytopharmacological Review on a Medicinal Plant: Juniperus communis. *International Scholarly Research Notices, 2014*(1), 634723. https://doi.org/10.1155/2014/634723

Buré, C. M., & Sellier, N. M. (2004). Analysis of the Essential Oil of Indonesian Patchouli (Pogostemon cabin Benth.) Using GC/MS (EI/CI). *Journal of Essential Oil Research, 16*(1), 17-19. https://doi.org/10.1080/10412905.2004.9698638

Chouhan, S., Sharma, K., & Guleria, S. (2017). Antimicrobial activity of some essential oils—present status and future perspectives. *Medicines, 4*(3). https://doi.org/10.3390/medicines4030058

CLSI. (2017). Performance Standards for Antimicrobial Susceptibility Testing Twenty-seventh informational supplement. M100-S27, Wayne, Pennsylvania.

Dechayont, B., Ruamdee, P., Poonnaimuang, S., Mokmued, K., & Chunthorng-Orn, J. (2017). Antioxidant and antimicrobial activities of Pogostemon cablin (Blanco) Benth. *Journal of Botany, 2017*(1), 8310275. https://doi.org/10.1155/2017/8310275

Donelian, A., Carlson, L. H. C., Lopes, T. J., & Machado, R. A. F. (2009). Comparison of extraction of patchouli (Pogostemon cablin) essential oil with supercritical CO2 and by steam distillation. *Journal of Supercritical Fluids, 48*(1), 15-20. https://doi.org/10.1016/j.supflu.2008.09.020

Dung, N., Leclercq, P., Thai, T., & Moi, L. (1990, 12–16 November 1989). Chemical composition of patchouli oil of Vietnam Proceedings of the International Congress of Essential Oils, Fragrances and Flavours, New Delhi, India.

Galovičová, L., Borotová, P., Valková, V., Ďúranová, H., Štefániková, J., Vukovic, N. L., Vukic, M., & Kačániová, M. (2022). Biological Activity of Pogostemon cablin essential oil and its potential use for food preservation. *Agronomy, 12*(2). https://doi.org/10.3390/agronomy12020387

Gonny, M., Cavaleiro, C., Salgueiro, L., & Casanova, J. (2006). Analysis of Juniperus communis subsp. alpina needle, berry, wood and root oils by combination of GC, GC/MS and 13C-NMR. *Flavour and Fragrance Journal, 21*(1), 99-106. https://doi.org/10.1002/ffj.1527

Gordien, A. Y., Gray, A. I., Franzblau, S. G., & Seidel, V. (2009). Antimycobacterial terpenoids from Juniperus communis L. (Cuppressaceae). *Journal of Ethnopharmacology, 126*(3), 500-505. https://doi.org/10.1016/j.jep.2009.09.007

Hasegawa, Y., Tajima, K., Toi, N., & Sugimura, Y. (1992). An additional constituent occurring in the oil from a patchouli cultivar. *Flavour and Fragrance Journal, 7*(6), 333-335. https://doi.org/10.1002/ffj.2730070608

Haziri, A., Faiku, F., Mehmeti, A., Govori, S., Abazi, S., Daci, M., Haziri, I., Bytyqi-Damoni, A., & Mele, A. (2013). Antimicrobial properties of the essential oil of Juniperus communis (L.) growing wild in east part of Kosovo. *American Journal of Pharmacology and Toxicology, 8*(3), 128. https://doi.org/10.3844/ajptsp.2013.128.133

Höferl, M., Stoilova, I., Schmidt, E., Wanner, J., Jirovetz, L., Trifonova, D., Krastev, L., & Krastanov, A. (2014). Chemical composition and antioxidant properties of juniper berry (juniperus communis l.) essential oil. action of the essential oil on the antioxidant protection of *Saccharomyces cerevisiae* model organism. *Antioxidants, 3*(1), 81-98. https://doi.org/10.3390/antiox3010081

Hu, L. F., Li, S. P., Cao, H., Liu, J. J., Gao, J. L., Yang, F. Q., & Wang, Y. T. (2006). GC–MS fingerprint of Pogostemon cablin in China. *Journal of Pharmaceutical and Biomedical Analysis, 42*(2), 200-206. https://doi.org/10.1016/j.jpba.2005.09.015

Junren, C., Xiaofang, X., Mengting, L., Qiuyun, X., Gangmin, L., Huiqiong, Z., Guanru, C., Xin, X., Yanpeng, Y., Fu, P., & Cheng, P. (2021). Pharmacological activities and mechanisms of action of Pogostemon cablin Benth: a review. *Chinese Medicine, 16*(1), 5. https://doi.org/10.1186/s13020-020-00413-y

Khaidem, A., Das, M. K., & Ningthoujam, S. S. (2025). Exploring the phytochemical and pharmacological properties of pogostemon oil: a critical review. *Annals of Multidisciplinary Research Innovation and Technology, 4*(1), 119-127.

Kuwagata, M., Doi, Y., Saito, H., Tsurumoto, M., Igarashi, T., Nishimura, T., Taquahashi, Y., Hirabayashi, Y., & Kitajima, S. (2024). A 90-day repeated oral dose toxicity study of p-cymene in rats. *Fundamental Toxicological Sciences, 11*(4), 169-181. https://doi.org/10.2131/fts.11.169

Linz, M. S., Mattappallil, A., Finkel, D., & Parker, D. (2023). Clinical impact of staphylococcus aureus skin and soft tissue infections. *Antibiotics, 12*(3).

Luo, J., Feng, Y., Guo, X., & Li, X. (1999). GC-MS analysis of volatile oil of herba Pogostemonis collected from Gaoyao county. *Zhong Yao Cai, 22*(1), 25-28.

Luo, J., Liu, Y., Feng, Y., Guo, X., & Cao, H. (2003). Two chemotypes of Pogostemon cablin and influence of region of cultivation and harvesting time on volatile oil composition. *Acta Pharmaceutica Sinica, 38*(4), 307-310.

Masrur, A. K. (2008). Microwave assisted extraction of patchouli essential oil using ethanol as solvent University Putra Malaysia. Serdang, Malaysia.

Maurya, A. K., Devi, R., Kumar, A., Koundal, R., Thakur, S., Sharma, A., Kumar, D., Kumar, R., Padwad, Y. S., Chand, G., Singh, B., & Agnihotri, V. K. (2018). Chemical Composition, Cytotoxic and Antibacterial Activities of Essential Oils of Cultivated Clones of Juniperus communis and Wild Juniperus Species. *Chemistry & Biodiversity, 15*(9), e1800183. https://doi.org/10.1002/cbdv.201800183

Mërtiri, I., Păcularu-Burada, B., & Stănciuc, N. (2024). Phytochemical characterization and antibacterial activity of albanian juniperus communis and juniperus oxycedrus berries and needle leaves extracts. *Antioxidants, 13*(3). https://doi.org/10.3390/antiox13030345

Murbach Teles Andrade, B. F., Nunes Barbosa, L., da Silva Probst, I., & Fernandes Júnior, A. (2014). Antimicrobial activity of essential oils. *Journal of Essential Oil Research, 26*(1), 34-40. https://doi.org/10.1080/10412905.2013.860409

Pandey, S. K., Gogoi, R., Bhandari, S., Sarma, N., Begum, T., Munda, S., & Lal, M. (2022). A comparative study on chemical composition, pharmacological potential and toxicity of Pogostemon cablin Linn., (Patchouli) Flower and Leaf Essential Oil. *Journal of Essential Oil Bearing Plants, 25*(1), 160-179. https://doi.org/10.1080/0972060X.2021.2013325

Pinho Mariana, G., Götz, F., & Peschel, A. (2025). Staphylococcus aureus: a model for bacterial cell biology and pathogenesis. *Journal of Bacteriology, 207*(8), e00106-00125. https://doi.org/10.1128/jb.00106-25

Polat Sağsöz, N., Güven, L., Gür, B., Cengiz, M., Vejselova Sezer, C., Orhan, F., & Barış, Ö. (2025). Potential of herbal essential oils as denture cleansers against biofilm formation on dental acrylic resin: in vitro and in silico approaches. *Journal of Chemistry, 2025*(1), 4595925. https://doi.org/10.1155/joch/4595925

Protox3. (August 14, 2025). https://tox.charite.de /protox3

PubChem (2025). https://pubchem.ncbi.nlm.nih.gov

Silva-Filho, S. E., Wiirzler, L. A. M., Cavalcante, H. A. O., Uchida, N. S., de Souza Silva-Comar, F. M., Cardia, G. F. E., da Silva, E. L., Aguiar, R. P., Bersani-Amado, C. A., & Cuman, R. K. N. (2016). Effect of patchouli (Pogostemon cablin) essential oil on in vitro and in vivo leukocytes behavior in acute inflammatory response. *Biomedicine & Pharmacotherapy, 84*, 1697-1704. https://doi.org/10.1016/j.biopha.2016.10.084

Srivastava, S., Lal, R. K., Singh, V. R., Rout, P. K., Padalia, R. C., Yadav, A. K., Bawitlung, L., Bhatt, D., Maurya, A. K., Pal, A., Bawankule, D. U., Mishra, A., Gupta, P., & Chanotiya, C. S. (2022). Chemical investigation and biological activities of Patchouli (Pogostemon cablin (Blanco) Benth) essential oil. *Industrial Crops and Products,*

188, 115504. https://doi.org/https://doi.org/10.1016/j.indcrop.2022.115504

Swamy, M. K., & Sinniah, U. R. (2015). A comprehensive review on the phytochemical constituents and pharmacological activities of Pogostemon cablin benth: An aromatic medicinal plant of industrial importance. *Molecules, 20*(5), 8521-8547. https://doi.org/10.3390/molecules20058521

SwissADME. (August 13, 2025). http://www.swissadme.ch/

Vasilijević, B., Knežević-Vukčević, J., Mitić-Ćulafić, D., Orčić, D., Franciković, M., Srdic-Rajic, T., Jovanović, M., & Nikolić, B. (2018). Chemical characterization, antioxidant, genotoxic and in vitro cytotoxic activity assessment of Juniperus communis var. saxatilis. *Food and Chemical Toxicology, 112*, 118-125. https://doi.org/10.1016/j.fct.2017.12.044