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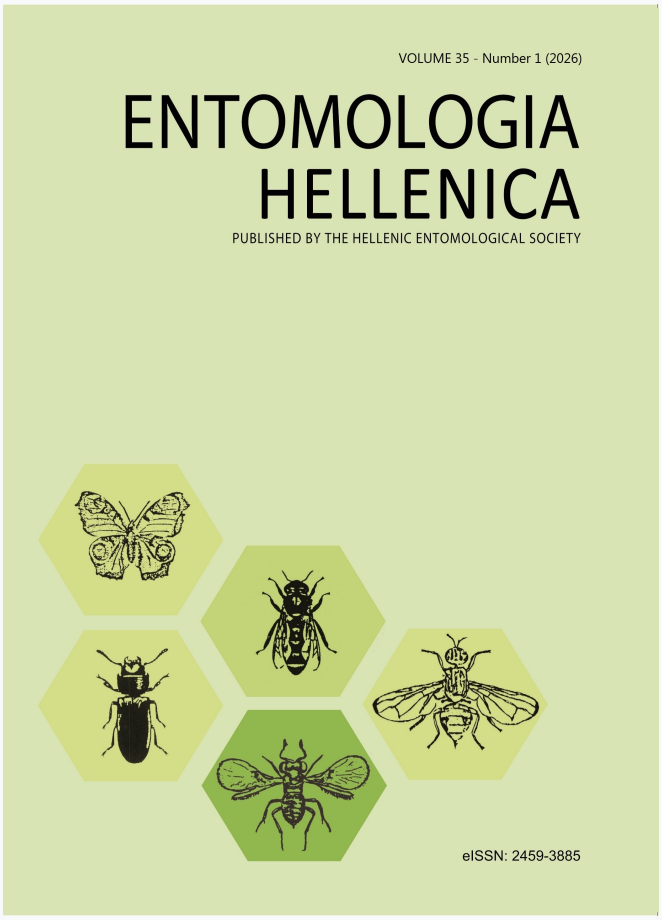

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Molecular docking evaluation of the insecticidal impacts of some essential oils' constituents

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ABSTRACT

For a sustainable agriculture, the use of biopesticides is among the main components of Integrated Pest Management. When compared to chemical pesticides, biopesticides derived from plants offers numerous benefits. Additionally, the use of *in silico* approach could assist researchers in reducing the duration and expense of *in vitro* experiments. In this context, the current study's objective is to predict the binding potential of *Salvia microphylla* (Lamiaceae) essential oils, in addition to two active ingredients of chemical pesticides, against two target proteins in insect, using molecular docking technique. *Via* MOE software, the best-scored position for every molecule was the only one achieved after the free binding energy (kcal/mol) was calculated. According to the results, the active molecules of conventional insecticides recorded the best results of binding interaction with the two examined target proteins (acetylcholinesterase and ecdysone receptor), followed by the molecule γ-eudesmol. The overall results indicated that among the tested compounds, the sesquiterpene γ-eudesmol was found to have the highest docking score with acetylcholinesterase and ecdysone receptors through the *in silico* study. Therefore, testing this ingredient on insects in both lab and field settings is strongly advised.

KEY WORDS: bio-insecticides, in silico, *Salvia microphylla*, target enzymes, γ-eudesmol.

Introduction

The need for the innovation of new insecticidal active ingredients is amplified by the advancements in agricultural yield and the management of disease vectors (Sparks and Bryant 2022). Besides, the quest for effective and environmentally sustainable insecticides has become increasingly crucial in the face of rising resistance to chemical pesticides and growing environmental concerns.

In ancient periods, herbs were greatly valued for their inherent health advantages and therapeutic qualities, rendering them essential components of medicinal practices. Among these esteemed herbs, *Salvia microphylla*, originating from the aromatic Lamiaceae family, which is known as the mint family, holds an important place (Trivedi et al. 2024). Numerous studies have highlighted the promising biological activities of *S. microphylla* in drug development, including neuroprotective effects (Ayoub et al. 2022), anti-mutagenic activity (Mathew and Thoppil 2012), anti-inflammatory and anti-oxidant activity (Choi et al. 2023) as well as

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insecticidal and juvenomimetic (Romo-Asunción et al. 2016), and aphicidal activities (Lebbal et al. 2023).

Exploring the interaction of essential oil (EO) components with molecular targets is crucial in deciphering why some possess different insecticidal qualities. Despite substantial experimental data supporting the properties of EOs, there is still much to uncover regarding their biochemical mechanisms of action (Ishaaya 2001). Computational tools play a significant role in this endeavor, aiding in the elucidation of how these natural compounds function (Da Costa et al. 2019). Several computational methodologies have effectively illustrated the mechanisms with which certain compounds in EOs function as inhibitors, including molecular docking approach (Corrêa et al. 2023). This latter is a structure-based drug design method that simulates the molecular interaction and predicts the binding mode between receptors and ligands (Morris and Lim-Wilby 2008). It may present many important advantages. For instance, *in silico* prediction of insect gut protease and Protease Inhibitors (PIs) interactions could minimize the cost and period of their *in vitro* screening (Ware et al. 2018).

Our approach involves compiling a comprehensive phytochemical profile of *S. microphylla*, followed by *in silico* molecular docking to predict the interaction of these compounds with known insecticidal targets. This methodology not only facilitates the identification of potential novel insecticidal compounds, but also contributes to a deeper understanding of the biological activities of this plant. This study aligns with the global shift towards sustainable and eco-friendly agricultural practices, highlighting the intersection of traditional botanical knowledge and cutting-edge computational research.

Materials and Methods

Determination of ligands: The purpose of the present *in silico* study is to assess the insecticidal potential of some compounds from *S. microphylla* EOs, in addition to two active molecules of chemical insecticides, Diazinon and Halofenozide, as possible inhibitors of acetylcholinesterase and ecdysone receptor proteins, respectively (IRAC, 2022). The chemical composition of the EOs was obtained from several articles (Lima et al. 2012; Satyal et al. 2020; Chouit et al. 2021). Subsequently, eighteen of their major compounds (based on their percentage abundance in the EO), were retrieved from PubChem database in SDF format.

Determination of Receptors: Two target proteins involved in different vital insect functions have been selected (Table 1). Acetylcholinesterase (AchE) is a key enzyme in the insect nervous system, in which the cholinergic system is essential, and this property led to the development of inhibitors of this enzyme as insecticides (Fournier et al. 1992). Whereas, the ecdysone receptor (EcR) has been an important target in the design of new, environmentally safe insecticides against pest species causing billions of pounds of damage to global agriculture each year (Billas et al. 2003).

X-ray structure complexed with their co-crystalized ligands of AChE (PDB code: 6XYU) deposited by Nachon et al. (2020) and EcR (PDB code: 1R1K) (Billas et al. 2003) was downloaded from the Protein Data Bank (http://www.rcsb.org/).

Table 1. Description of the target proteins.

Target enzyme	**PDB Code**	**Classification**	**Ligand**
AChE from *Drosophila melanogaster* complex with tacrine derivative 9-(3-iodobenzylamino)-1,2,3,4-	6XYU	Hydrolase	I40
Crystal structure of the ligand-binding domains of the heterodimer EcR/USP	1R1K	Hormone/ Growth factor receptor	P1A EPH

Ligand and Receptor Preparation: In order to facilitate the interaction of single inhibitors or ligands with the selected receptor, the ligands and receptor were prepared for docking by minimizing their energy and then protonating them in 3D using the MOE (Molecular Operating Environment) software package, version 2019.0102, developed by Chemical Computing Group Inc. (Canada). This software was installed on an Intel computer running Microsoft Windows, equipped with an Intel® Core™ i3 CPU M370 @ 2.40 GHz and 8 GB of RAM.

All receptors were freed from unwanted water molecules and heteroatoms enabling the interaction of just inhibitors or ligands with the designated receptor. Protonation states were determined at pH 7.0 utilizing MOE's Protonate 3D module, which takes into account the local environment and hydrogen bonding. Ligand tautomers and protomers were produced and optimized using the Wash and Protonate 3D tools. The active site was delineated according to the location of the co-crystallized ligand, employing a cubic grid box measuring 12 × 12 × 12 Å, centered on the ligand identified in the crystal structure. Energy minimization of proteins and ligands was conducted with the MMFF94x and AMBER99 force field for ligands and receptors, respectively with a gradient cutoff of 0.5 kcal/mol/Å.

Validation of docking process: Redocking the native ligand on the target protein validated the docking process. The findings display the compound with the lowest binding energy when it interacts with the target protein to determine the docking compound's RMSD (root-mean-square deviation) value. If the RMSD value is less than 2 Å, the approach is considered valid, and the test drug and target protein can be docked at the same site (Cosconati et al. 2010).

Receptor-Ligand Docking: The docking site was identified as the binding site of co-crystalized ligand, and the rigid receptor docking methodology and triangle matcher placement approach were used to dock the database comprising every evaluated chemical. Docking simulations utilized Triangle Matcher for placement, first scoring with London dG, subsequently refined with GBVI/WSA dG. Twenty unique docking simulations ("replicas") were conducted for each ligand to thoroughly explore binding conformations. The highest-ranked postures underwent post-docking reduction utilizing the AMBER99 force field (500 iterations, with a gradient cut-off of 0.05 kcal/mol/Å). The optimal pose was determined by the lowest GBVI/WSA dG score following minimization.

Moreover, the *in silico* evaluation of ADME and Toxicological profiles of EOs compounds from *S. microphylla* was performed using SwissADME (Daina et al. 2017), pkCSM (Pires et al. 2015), and ProTox-3.0 (Banerjee et al. 2024).

Results and Discussion

Results showed that, following the result of Diazinon and Halofenozide, the molecule γ-eudesmol (CID- 6432005) exhibited the lowest binding energy toward the proteins 6XYU and 1R1K (for P1A ligand site), with -5.80 and -6.92 kcal/mol (Table 2). Whereas, T-cadinol (CID-160799) had the best result of the binding energy with the protein 1R1K (when considering EPH ligand site), after the S score of Halofenozide. The overall results of the molecular docking of the present study suggest that γ-eudesmol revealed the best inhibitory potential for the two studied target enzymes.

Concerning thermodynamic characteristics, we studied hydrophobic and electrostatics interactions between the best EOs compound (γ-eudesmol) and the target enzyme 1R1K (for P1A ligand). The Figure 1 showed slightly dominance of lipophilic interaction between the protein and the ligand, highlighted by the presence of green color.

Besides, the electrostatic interaction between the target and the best ligand is characterized by a mix of different charges (Figure 2).

Moreover, the study of the interactions between the enzyme 1R1K and the best EOs molecule revealed close links between γ-

eudesmol and the following amino acids: GLU309 (H-donor, distance= 2.62 Å), ARG383 (H-acceptor, distance= 2.63 Å) and THR346 (H-donor, distance= 2.84 Å) (Figure 3).

Table 2: S score of the tested ligands with the target proteins.

Ligand	**PubChem CID**	**6XYU dock results**	**1R1K dock results** (P1A ligand)	**1R1K dock results** (EPH ligand)
Active molecule of chemical pesticides	3017/ 114994	-7.34	-7.84	-6.48
γ-eudesmol	6432005	-5.80	-6.92	-4.65
T-cadinol	160799	-5.60	-6.05	-5.57
δ-cadinene	441005	-5.30	-6.44	-5.08
1,8 cineole (eucalyptol)	2758	-3.45	-5.43	-4.48
Camphor	2537	-3.09	-5.47	-4.06
α-gurjunene	15560276	-5.30	-6.15	-5.14
α-humulene	5281520	-5.29	-6.15	-4.91
Allo-aromadendrene	42608158	-4.44	-6.28	-4.61
γ-cadinene	92313	-5.21	-6.05	-4.97
β-phellandrene	11142	-5.00	-5.44	-4.28
α-eudesmol	92762	-5.14	-6.86	-4.50
Bornyl acetate	93009	-3.69	-6.33	-4.61
(*E*)-Caryophyllene	5281515	-3.93	-6.27	-4.90
Aromadendrene	91354	-4.65	-6.32	-4.69
Bicyclogermacrene	13894537	-5.46	-5.97	-4.57
Spathulenol	92231	-4.46	-6.28	-4.43
Caryophyllene oxide	1742210	-4.74	-6.60	-5.20
β-eudesmol	91457	-4.72	-6.73	-5.02

The first step of molecular docking is to align the flexible ligand with the rigid macromolecule and then evaluate, with a scoring function their binding energy (Wolber and Langer 2005). There are three basic tasks any docking procedure must accomplish: (1) characterization of the binding site; (2) positioning of the ligand into the binding site; and (3) evaluating the strength of interaction for a specific ligand-receptor complex ("scoring") (Krumrine et al. 2003). In our case, the lowest S score

among S. *microphylla* EO compounds was recorded for the sesquiterpene γ-eudesmol in binding with 1R1K (-6.92 kcal/mol). This molecule was identified previously, among the most toxic compounds against *Meloidogyne incognita* nematodes (Ntalli et al. 2011).

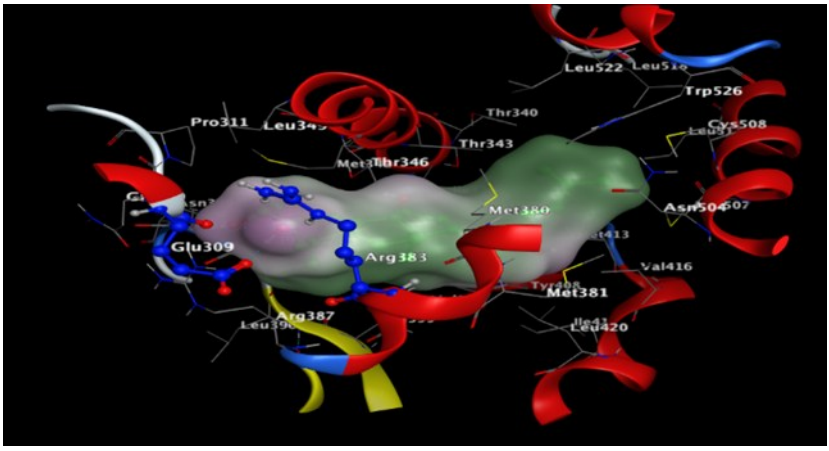

FIG. 1: Lipophilic interactions between γ-eudesmol and the active site of 1R1K.

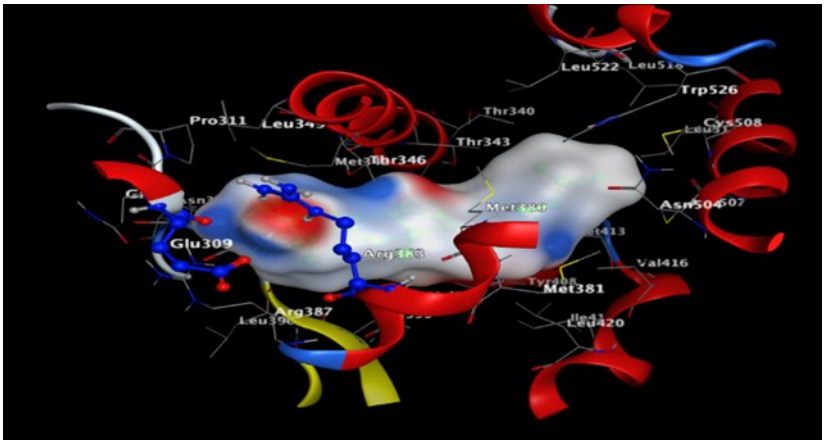

FIG. 2: Electrostatic interactions between γ-eudesmol and the active site of 1R1K.

The use of molecular docking had gained a rise in attention recent years, in order to evaluate the insecticidal and acaricidal effects of many compounds. The molecular docking study of the newly synthesized quinoxaline derivatives registered that compound 16, which is the most toxicological agent against nymphs of cowpea aphids, had the highest binding score (−10.54 kcal/mol) compared to the other synthesized pyrimidine and thiazolidinone derivatives (Alanazi et al. 2022). Moreover, a molecular docking study of Valectin (a lectin of *Vigna aconitifolia*) against alanyl amino peptidase n (APn) receptor of *Acyrthosiphon pisum* aphid, revealed that ASP159, SER161, GLU164, SER181, ASN178, VAL177, SER35, VAL94, ASN92, LYS141, ARG85, GLU138 and TYR139 residues of Valectin are critical for the in-

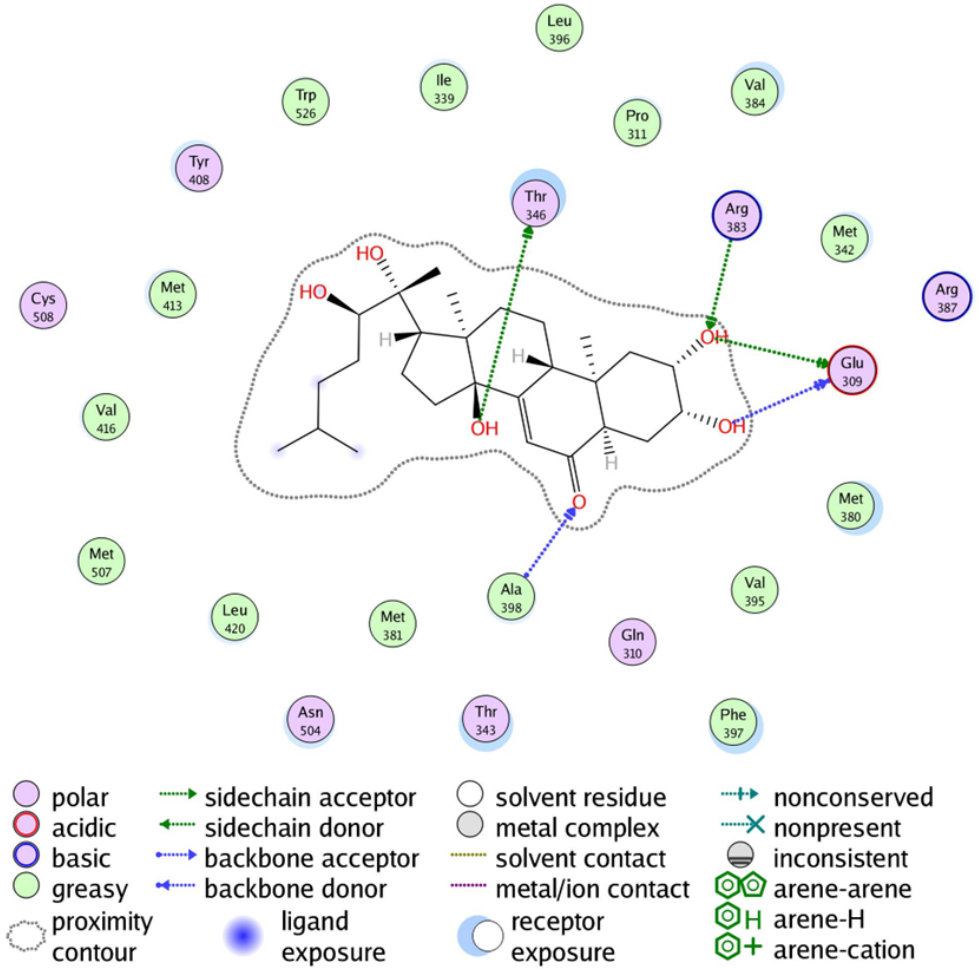

FIG. 3: Amino acids interactions in the binding site between γ-eudesmol and 1R1K protein.

teraction with insect receptor (Prajapat et al. 2020).

In addition, the use of molecular docking in numerous recent papers indicated a potential bioactivity against Lepidopteran insects of some compounds, such as Cry4Ba (Saonerkar et al. 2022), Cry11Aa from *Bacillus thuringiensis* (Abdul Halim and Hussin 2022), and citronellal compounds from *Cymbopogon nardus* (citronella) (Firdausiah et al. 2022).

On the other hand, Belhadji et al. (2022) propose, based on molecular docking results, the Schottenol molecule extracted from essential oils of *Argania spinosa* as a possible new inhibitor of the parasitic mite *Varroa destructor*.

Pharmacokinetic analysis (Table 3) reveals high intestinal absorption across the compound set (>90%), with sesquiterpenes exhibiting particularly favorable characteristics, and predicts substantial blood–brain barrier penetration (Log BB = 0.3–0.8), suggesting a strong potential for CNS activity attributable to the compounds' inherent lipophilicity.

Table 3. In silico predicted ADME properties of the compounds from *Salvia microphylla* essential oils.

Properties	Absorption	Distribution			Metabolism					Excretion
Models	Intestinal absorption (human)	VDss (human)	BBB per-meability	CNS per-meability	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Total Clearence
Unity	% absorbed	Log L.Kg^{-1}	Log BB	Log PS	Yes/No	Yes/No	Yes/No	Yes/No	Yes/No	Log mL.min^{-1}. kg
Diazinon	92.749	-0.348	-0.438	-3.029	No	No	No	No	Yes	0.391
Halofenozide	93.496	-0.056	0.069	-1.718	Yes	Yes	Yes	No	Yes	-0.272
γ-eudesmol	92.234	0.487	0.581	-2.299	No	Yes	Yes	No	No	1.027
T-cadinol	94.296	0.42	0.596	-2.151	No	No	No	No	No	1.085
δ-cadinene	96.128	0.689	0.773	-1.945	No	No	No	No	No	1.182
1,8 cineole	96.505	0.491	0.368	-2.972	No	No	No	No	No	1.009
Camphor	95.965	0.331	0.612	-2.158	No	No	No	No	No	0.109
α-gurjunene	96.566	0.786	0.792	-2.136	No	No	Yes	No	No	0.907
α-humulene	94.682	0.505	0.663	-2.555	No	No	No	No	No	1.282
Allo-aromadendrene	95.302	0.753	0.822	-1.769	No	No	No	No	No	0.926
γ-cadinene	96.475	0.67	0.809	-1.631	No	No	No	No	No	1.118
β-phellandrene	96.045	0.393	0.747	-2.023	No	No	No	No	No	0.196
α-eudesmol	93.22	0.486	0.594	-2.309	No	Yes	No	No	No	1.03
Bornyl acetate	95.366	0.307	0.553	-2.399	No	No	No	No	No	1.029
E)-Caryophyllene	94.845	0.652	0.733	-2.172	No	No	No	No	No	1.088
Aromadendrene	95.302	0.753	0.822	-1.769	No	No	No	No	No	0.926
Bicyclogermacrene	95.014	0.648	0.716	-2.332	Yes	No	No	No	No	1.09
Spathulenol	93.906	0.569	0.617	-2.526	No	Yes	Yes	No	No	0.895
Caryophyllene oxide	95.421	0.586	0.654	-2.508	Yes	Yes	Yes	No	No	0.905
β-eudesmol	94.296	0.459	0.634	-1.858	No	No	No	No	No	1.032

None of the principal components functioned as inhibitors of CYP2D6 or CYP3A4, indicating a negligible probability of substantial metabolic interactions—a favorable pharmacokinetic characteristic. Some substances, such as spathulenol and caryophyllene oxide, operated as suspected CYP1A2 or CYP2C9 inhibitors. Excretion parameters, indicated by total clearance values approaching 1 log mL min^{-1} kg^{-1}, signify moderate elimination rates, implying an ideal equilibrium between metabolic stability and detoxifying capacity. In summary, these findings suggest that S. *microphylla* volatiles are interesting candidates with ADME characteristics that are equivalent to those of well-known bioactive terpenes.

Table 4: In silico predicted toxicity of the compounds from *S. microphylla* EOs.

Proprieties	Toxicity						
Models	hERG I inhibitor	hERG II inhibitor	AMES toxicity	Oral toxicity		Hepato-toxicity	Skin sensi-tization
				(LD_{50})	Class		
Unity	Yes/No	Yes/No	Yes/No	mg/Kg	/	Yes/No	Yes/No
Diazinon	No	No	No	17	2	Yes	No
Halofenozide	No	No	Yes	1400	4	Yes	No
γ-eudesmol	No	No	No	4300	5	No	Yes
T-cadinol	No	No	No	2830	5	No	Yes
δ-cadinene	No	No	No	4390	5	No	Yes
1,8 cineole	No	No	No	2480	5	No	Yes
Camphor	No	No	No	775	4	No	Yes
α-gurjunene	No	No	No	5000	5	No	No
α-humulene	No	No	No	3650	5	No	Yes
Allo-	No	No	No	5000	5	No	No
γ-cadinene	No	No	No	4400	5	No	Yes
β-phellandrene	No	No	No	5000	5	No	Yes
α-eudesmol	No	No	No	5000	5	No	Yes
Bornyl acetate	No	No	No	3100	5	No	Yes
E)-	No	No	No	5300	5	No	Yes
Aromaden-	No	No	No	5000	5	No	No
Bicycloger-macrene	No	No	No	5300	5	No	Yes
Spathulenol	No	No	No	3900	5	No	Yes
Caryophyllene	No	No	No	5000	5	No	Yes
β-eudesmol	No	No	No	2000	4	No	Yes

The toxicological evaluation conducted supports the safety profile of *S. microphylla* EO constituents. These results not only substantiate the pharmacological efficacy of *S. microphylla* EOs, but also reinforce their suitability as lead scaffolds for the development of plant-derived pesticides and therapeutic agents. Accordingly, the convergence of physicochemical compatibility, robust ADME characteristics, and minimal observed toxicity positions *S. microphylla* EOs as exceptionally promising candidates for applications in pharmaceutical formulation as well as in the advancement of environmentally sustainable pest control solutions.

In addition, field and laboratory bioassays are indispensable to confirm the current findings.

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