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α-Glucosidase Inhibitory Activity of Compounds from the Essential Oil of *Leucas lavandulifolia* Sm.: Insights from GC-MS Analysis and Molecular Docking Studies

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Diabetes, a chronic metabolic disorder, characterized by elevated blood sugar levels is a burning issue of the 21st century. This problem can be managed by inhibiting the normal functioning of the α-glucosidase enzyme. This study aims to identify the molecules present in the oil of *Leucas lavandulifolia* Sm. using GC-MS analysis and to identify potential α-glucosidase inhibitors through computational approaches. The results of GC-MS demonstrated the presence of 28 different phytocompounds. From molecular docking calculations, copaborneol and 3-alpha-hydroxy-manool exhibited binding affinities of -9.2 kcal/mol and -8.7 kcal/mol, respectively, surpassing that of the native ligand (alpha-maltose, -8.6 kcal/mol) and reference drugs (voglibose and miglitol), while methyl 8-pimaren-18-oate showed a binding affinity of -8.4 kcal/mol, comparable to that of the native ligand. The drug-likeness and toxicity prediction from server-based calculations suggested the drug-like properties of hit candidates as their properties were comparable with that of the reference drugs. Thus, after further *in silico* computation, *in vivo*, and *in vitro* experiments, the hit molecules could potentially be used as prospective α-glucosidase inhibitors for diabetes management.

Keywords: Essential oil; molecular docking; scoring function; ADMET.

1. INTRODUCTION

Plants serve as natural sources of numerous elements (alkaloids, flavonoids, minerals) with the capacity to alleviate various diseases [1]. Humans have traditionally utilized natural remedies to treat and prevent a wide range of diseases, and these have been the primary sources of therapeutics before the development of the modern allopathic medicine system [2]. The World Health Organization (WHO) estimates that 80% of people in developing countries still depend on traditional approaches to medications [3, 4]. Recently, plants have been getting attention worldwide as a source of treatment due to their natural origin, availability in local communities, cost-effectiveness, and having fewer side effects than modern drugs. Medicinal plants contain active plant materials or secondary metabolites that are used for effective and robust medications [5].

Leucas lavandulifolia Sm. (*L. lavandulifolia*) is an annual herb that belongs to the Lamiaceae family, and is commonly known as lavender-leaved Leucas and Guma or Ghaante Phool in Nepali [6]. It is predominantly found in tropical and sub-tropical regions as a weed in cultivated lands, roadsides, and wastelands [7]. This plant has been used by traditional healers to treat a wide range of diseases and health conditions like snake bites, migraine, colds, coughs, and abdominal discomforts [8]. It is also used as an anthelmintic against roundworms and to treat rheumatism, psoriasis, and leg sores. Various chemical constituents like taraxerone, linifoliol, lupeol, chrysoeriol, and acacetin are reported to be present in the plant [9]. Due to the presence of such secondary metabolites, *L. lavandulifolia* has been reported to have multiple biological effects like antimicrobial, antioxidant, antipyretic, antidiarrheal, hepatoprotective, and hypoglycemic activities [10].

Diabetes mellitus (DM) is a chronic metabolic condition characterized by elevated blood sugar levels and disruptions in the metabolism of fats, carbohydrates, and proteins [11]. In recent years, the prevalence of DM has been consistently rising globally. According to a 2018 report by the WHO, more than 422 million people worldwide are affected by diabetes, and it is projected that over 418 million more individuals will be impacted by DM in the near future [12]. Among the various types of DM, Type 2 diabetes mellitus (T2DM), characterized by chronic metabolic imbalance, insulin resistance, and beta-cell failure, is the most prevalent, making up over 90% of all DM cases [13].

Molecular docking is a powerful technique employed in the discovery of potential lead compounds for diabetes management [14]. The computational approach for drug discovery has

proven to be a reliable, cost-efficient, and time-saving method for identifying and optimizing potent lead compounds [15]. This method predicts how molecules bind effectively with targets such as enzymes and receptor proteins [16, 17]. This research work aims to use a molecular docking approach for evaluating the α-glucosidase inhibitory activity of the compounds obtained from the GC-MS analysis of the oil of *L. lavandulifolia*. It tends to provide a foundational basis for further experiments in the drug design and discovery process.

2. MATERIALS AND METHODS

2.1 Plant Sample Collection and Extraction of Essential Oil

The parts of the plant *L. lavandulifolia* (leaves, flowers, and seeds) were collected from Nawalpur 45306, Nepal, and verified by the National Herbarium and Plant Laboratories (KATH), Lalitpur 44700, Nepal (voucher code P1 KATH155256). Essential oil from the fresh plant sample was extracted through hydro-distillation using the Clevenger apparatus at 100 °C for 6 h [18].

2.2 GC-MS Experiment

Gas chromatography-mass spectrometry (GCMS) experiment was performed using a GCMS-QP 2010 instrument. For the analysis, an SH-RTX-5MS capillary column was used (60 m × 0.32 mm × 0.25 µm) with a 95% dimethyl polysiloxane and 5% diphenyl stationary phase. Helium was used as carrier gas with a pressure of 53.8 kPa, total gas flow of 112.3 mL/min, and column flow of 1.35 mL/min. The GC-MS system began with an initial oven temperature of 50 °C for 1 minute, then increased to 230 °C at a rate of 3 °C per minute. Mass spectral detection was conducted in electron ionization mode, scanning from 40 to 350 m/z. The chemical constituents of the essential oils were identified by comparing their mass spectral fragmentation patterns to those in the National Institute of Standards and Technology (NIST) 2017 library and the Flavor and Fragrance Natural and Synthetic Compounds (FFNSC) 4.0 library [19].

2.3 *In silico* Approach

2.3.1 Selection and preparation of ligands and protein

The three-dimensional structures (sdf files) of 28 ligands identified in the oil of *L. lavandulifolia* were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and they were converted to pdbqt format for docking [20]. The 3D structure of the α-glucosidase protein with PDB ID: 5ZCC (X-ray resolution= 1.70 Å, expression system: *Escherichia coli*) (https://doi.org/10.2210/pdb5ZCC/pdb) were obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (https://www.rcsb.org/). The protein was first processed using the PyMOL program [21] to clean it, then hydrogen atoms were added, and it was saved in pdbqt format.

2.3.2 Molecular docking

The Molecular docking studies were carried out by using the AutoDock Vina software [20]. Parameters such as the grid center (-0.655, 53.715, 72.724), a box size of 30×30×30 Å^3, an energy range (difference between highest and lowest score) of 4 kcal/mol, 20 modes (optimum number of poses to be generated considering the accuracy desired and time consumed), and an exhaustiveness of 64 were employed for the docking process. The coordinates of the grid center were determined from the orthosteric pocket as visualized in the holo form of the crystal. The volume corresponding to the box size was large enough to fit the pool of the test molecules and to provide rotational degrees of freedom completely confined to it. The best protein-ligand complex with maximum binding affinity was determined and their 2D interactions were visualized using the Biovia Discovery Studio program [22]. The validation of the docking protocol was done by obtaining the heavy atom RMSD of 0.50 Å and the superimposition of the docked ligand with the native ligand (Fig. 1). The value below 2.00 Å is considered good and the search algorithm is deemed capable of capturing the minima [23].

2.3.3 ADMET prediction

The canonical SMILES retrieved from PubChem for each compound were uploaded to the ADMETlab 2.0 (https://admetmesh.scbdd.com/) and pkCSM (https://biosig.lab.uq.edu.au/pkcsm/) servers and their ADMET properties (absorption, distribution, metabolism, excretion, and toxicity) were analyzed [24, 25].

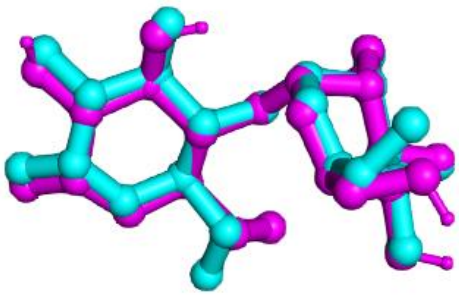


Fig. 1. Superimposition of the native ligand (cyan) in crystal structure with the docked ligand (magenta) obtained from calculations (RMSD= 0.50 Å)

3. RESULTS AND DISCUSSION

3.1 GC-MS Analysis

The analysis of the GC-MS chromatogram revealed 28 peaks in the oil of *L. lavandulifolia* (Fig. 2). It showed the presence of 28 compounds with methyl 8-pimaren-18-oate being the most prevalent one, constituting 37.09% of the area percentage (Table 1). The mass spectra and chemical structures of each phytocompound are depicted in the supplementary information (Fig. S1 and S2).

3.2 Molecular Docking Scores

Molecular docking calculations were utilized to evaluate the possibility and compatibility of interactions between a ligand (guest) and protein (host) in a complex and to determine the optimal binding pose of the ligands within the receptor protein's active site based on binding affinity [26]. The results revealed copaborneol and 3-alpha-hydroxy-manool as the top two candidates with binding affinities -9.2 kcal/mol and -8.7 kcal/mol, respectively, better than that of native ligand (-8.6 kcal/mol) and reference drugs (Table 2). It could be due to stronger and more stable binding interactions present between the ligand and the key amino acid residues surrounding it. Similarly, methyl 8-pimaren-18-oate has a binding affinity of -8.4 kcal/mol which is comparable with that of native ligand. The binding affinities indicated that the ligands were docked at the protein's active site and hence, the compounds obtained from *Leucas lavandulifolia* might inhibit the normal functioning of α-glucosidase.

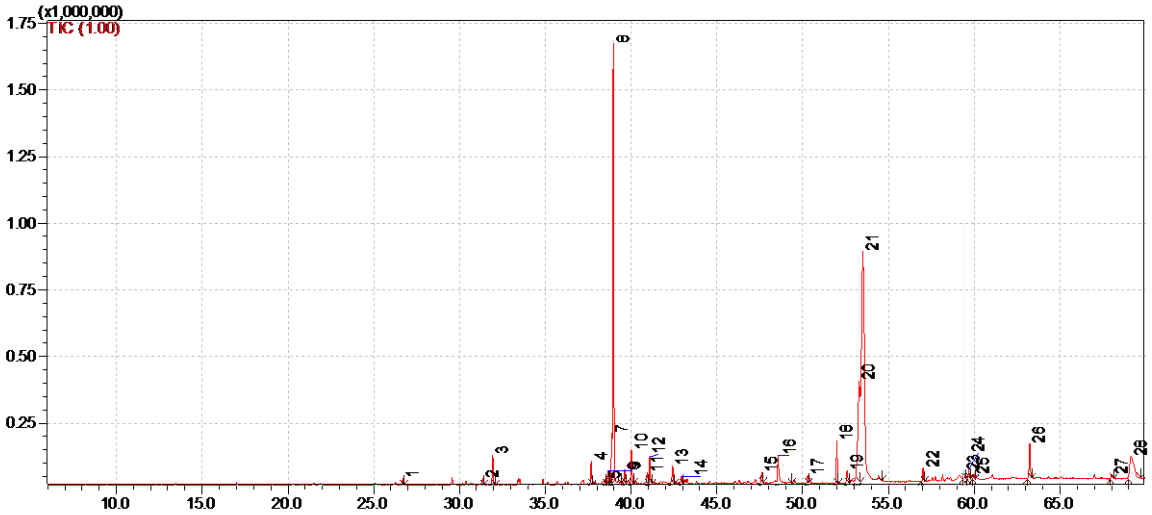


Fig. 2. Chromatogram of essential oil of *Leucas lavandulifolia* Sm.

Table 1. Compounds identified in the essential oil of *L. lavandulifolia*

Peak number	Name of compounds	Molecular formula	Molecular weight (g/mol)	Retention time (min)	Area%
1	n-Decanal	$C_{10}H_{20}O$	156.26	26.69	0.34
2	E-Caryophyllene	$C_{15}H_{24}$	204.35	31.357	0.35
3	Z-Caryophyllene	$C_{15}H_{24}$	204.35	31.933	1.48
4	14-hydroxy-4,5-dihydro-Caryophyllene	$C_{15}H_{26}O$	222.37	37.677	1.28
5	Octyl 2-methylbutyrate	$C_{13}H_{26}O_2$	214.34	38.486	0.38
6	Beta-Elemene	$C_{15}H_{24}$	204.35	38.646	0.75
7	Allo-Aromandendrene epoxide	$C_{15}H_{24}O$	220.35	38.87	2.3
8	Caryophyllene oxide	$C_{15}H_{24}O$	220.35	38.965	22.06
9	Copaborneol	$C_{15}H_{26}O$	222.37	39.639	0.81
10	Humulene epoxide II	$C_{15}H_{24}O$	220.35	40.027	1.7
11	14-hydroxy-(Z)-Caryophyllene	$C_{15}H_{24}O$	220.35	40.938	0.68
12	Caryophylla-4(12),8(13)-dien-5-alpha-ol	$C_{15}H_{24}O$	220.35	41.087	1.5
13	14-hydroxy-9-epi-(E)-caryophyllene	$C_{15}H_{24}O$	220.35	42.423	1.22
14	4,8-Dimethyl-4,9-decadienal	$C_{12}H_{20}O$	180.29	42.93	0.4
15	Mentha-1(7),8-dien-2-ol	$C_{10}H_{16}O$	152.23	47.612	0.59
16	Phytone	$C_{18}H_{36}O$	268.5	48.57	2.16
17	Drimenol	$C_{15}H_{26}O$	222.37	50.301	0.4
18	Larixol	$C_{20}H_{34}O_2$	306.5	51.99	2.22
19	Pentadecylic acid	$C_{15}H_{30}O_2$	242.4	52.59	0.96
20	Valerianol	$C_{15}H_{26}O$	222.37	53.298	12.09
21	Methyl 8-pimaren-18-oate	$C_{21}H_{34}O_2$	318.5	53.514	37.09
22	n-Heptadecane	$C_{17}H_{36}$	240.5	57.014	0.68
23	Torulosol	$C_{20}H_{34}O_2$	306.5	59.404	0.4
24	3-alpha-hydroxy-manool	$C_{20}H_{34}O_2$	306.5	59.683	0.52
25	Avobenzone	$C_{20}H_{22}O_3$	310.4	59.981	0.36
26	n-Nonadecane	$C_{19}H_{40}$	268.5	63.236	2.19
27	Javanol	$C_{15}H_{26}O$	222.37	68.032	0.4
28	n-Docosane	$C_{22}H_{46}$	310.6	69.148	4.71

Table 2. Binding affinities of different compounds obtained from GCMS analysis of *L. lavandulifolia* oil along with native and reference drugs with α-glucosidase protein (PDB ID: 5ZCC)

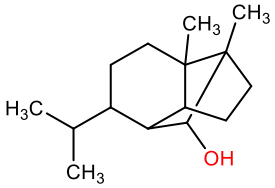
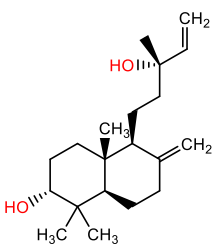
Ligands	PubChem CID	Binding affinity (kcal/mol)
Copaborneol	12303891	-9.2
3-alpha-hydroxy-manool	91750212	-8.7
Methyl 8-pimaren-18-oate	288361	-8.4
Valerianol	9859337	-7.9
Avobenzone	51040	-7.7
n-Docosane	12405	-7.7
Larixol	6708759	-7.4
Javanol	22096564	-7.4
Torulosol	349315	-7.3
14-hydroxy-9-epi-(E)-caryophyllene	5352484	-7.2
Caryophyllene oxide	1742210	-7.0
Drimenol	3080551	-6.8
14-hydroxy-4,5-dihydro- Caryophyllene	14238887	-6.8
Caryophylla-4(12),8(13)-dien-5-alpha-ol	91753606	-6.7

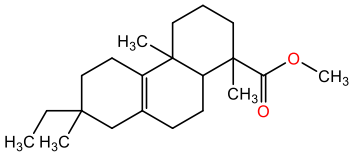
Ligands	PubChem CID	Binding affinity (kcal/mol)
Humulene epoxide II	10704181	-6.6
Beta-Elemene	6918391	-6.6
Z-Caryophyllene	6429301	-6.4
Allo-Aromandendrene epoxide	91746712	-6.4
Mentha-1(7),8-dien-2-ol	6429040	-6.4
E-Caryophyllene	5281515	-6.3
14-hydroxy-(Z)-Caryophyllene	6430534	-6.3
Phytone	10408	-6.1
n-Nonadecane	12401	-6.1
4,8-Dimethyl-4,9-decadienal	116736	-6.0
Pentadecylic acid	13849	-5.7
Octyl 2-methylbutyrate	520455	-5.7
n-Heptadecane	12398	-5.1
n-Decanal	8175	-5.0
Native	439341	-8.6
Voglibose	444020	-6.1
Miglitol	441314	-5.5

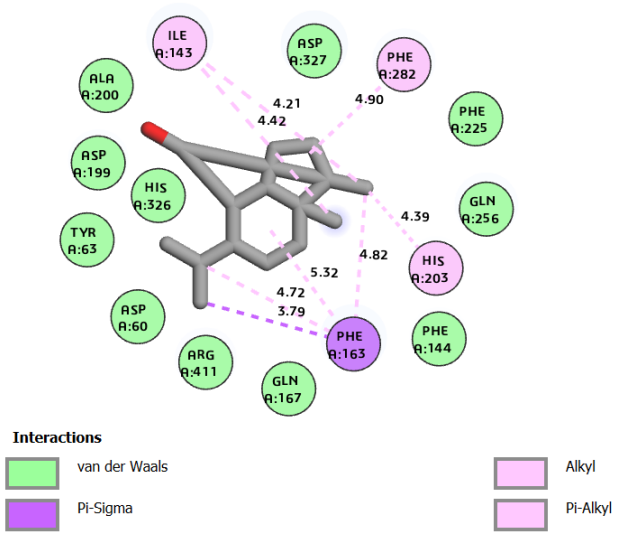
3.3 Protein-Ligand Interactions

Different types of interactions like Hydrogen bonds, Pi-Sigma, Pi-Alkyl, Alkyl, and van der Waals were observed between the ligands and amino acid residues of the protein (Fig. 3, Table 3). Copaborneol showed only hydrophobic interactions whereas 3-alpha-hydroxy-manool and Methyl 8-pimaren-18-oate demonstrated both hydrophilic and hydrophobic interactions. The amino acid residue PHE163 exhibited both Pi-sigma and Pi-Alkyl interactions, and ILE143 showed alkyl interactions with all three ligands. A conventional hydrogen bond and carbon-hydrogen bond were formed between methyl 8-pimaren-18-oate and amino acid residues; GLN328 and ASP327, respectively. Similarly, ASP199 formed a conventional hydrogen bond with 3-alpha-hydroxy-manool. The Pi-Alkyl interaction was observed with HIS103 and HIS326 with ligands 3-alpha-hydroxy-manool and methyl 8-pimaren-18-oate. Numerous van der Waals interactions were noted between the amino acid residues and the ligands. The top three ligands exhibited various hydrophobic and hydrophilic interactions with the key amino acid residues (having a significant role in the catalytic action), which could possibly disrupt or inhibit the normal functioning of α-glucosidase.

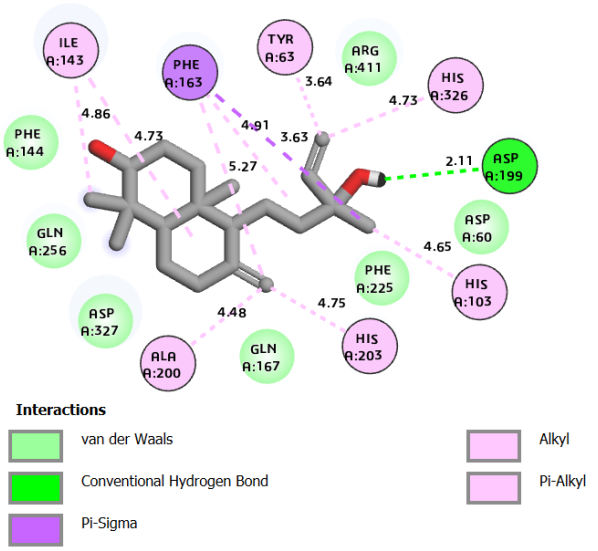
Table 3. Types of interactions between the top three ligands and amino acid residues of α-glucosidase, along with their respective distances (Å)

Ligands	Chemical Structures	Type of interactions	Active site residues (Distance Å)
Copaborneol		Pi-Sigma	PHE163 (3.79)
		Alkyl	ILE143 (4.21, 4.42)
		Pi-Alkyl	PHE163 (4.72, 4.82, 5.32), HIS203 (4.39), PHE282 (4.90)
		van der Waals	ASP60, TYR63, PHE144, GLN167, ASP199, ALA200, PHE225, GLN256, HIS326, ASP327, ARG411
3-alpha-hydroxy-manool		Hydrogen Bond	ASP199 (2.11)
		Alkyl	ILE143 (4.73, 4.86), ALA200 (4.48)
		Pi-Alkyl	TYR63 (3.64), HIS103 (4.65), PHE163 (4.91, 5.27), HIS203 (4.75), HIS326 (4.73)
		Pi-Sigma	PHE163 (3.63)
		van der Waals	ASP60, PHE144, GLN167,

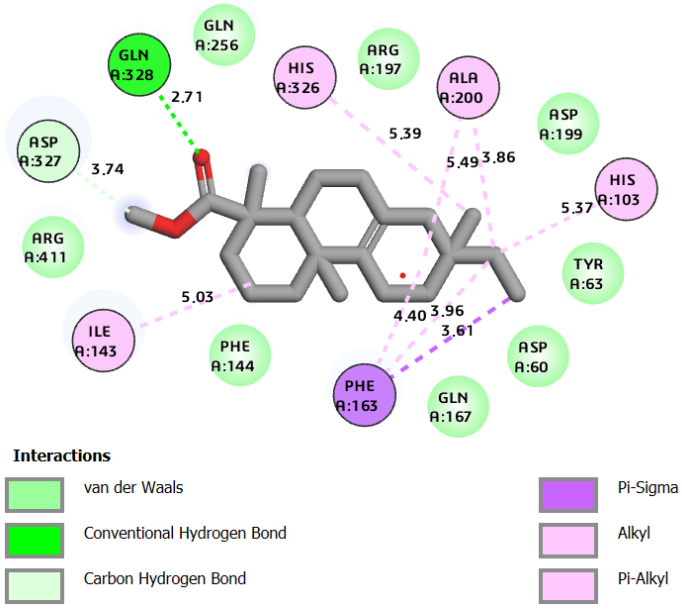
Ligands	Chemical Structures	Type of interactions	Active site residues (Distance Å)
			PHE225, GLN256, ASP327, ARG411
Methyl 8-pimaren-18-oate		Hydrogen Bond	GLN328 (2.71)
		Carbon Hydrogen Bond	ASP327 (3.74)
		Alkyl	ILE143 (5.03), ALA200 (3.86, 5.49)
		Pi-Alkyl	HIS103 (5.37), PHE163 (3.96, 4.40), HIS326 (5.39)
		Pi-Sigma	PHE163 (3.61)
		van der Waals	ASP60, TYR63, PHE144, GLN167, ARG197, ASP199, GLN256, ARG411



Copaborneol



3-alpha-hydroxy-manool



Methyl 8-pimaren-18-oate

Fig. 3. 2D interactions of top three ligands with α-glucosidase (PDB ID: 5ZCC)

3.4 Drug-likeness and Safety Profile

The pharmacodynamic (enzyme inhibition) and pharmacokinetic properties of hit candidates were predicted using *in silico* tools to assess their drug-likeness and suitability for human use (Table 4). The ADMET prediction showed that all hit molecules adhered to Lipinski's rule of five (RO5), suggesting they possess drug-like properties and are possibly suitable for human consumption. The compounds did not exhibit signs of AMES toxicity, hepatotoxicity, skin sensitization, or genotoxicity, analogous to that of the reference drugs, miglitol, and voglibose. Two hit candidates, copaborneol and methyl 8-pimaren-18-oate penetrated the blood-brain barrier (BBB) whereas 3-alpha-hydroxy-manool did not cross the barrier similar to that of the reference drugs. The metabolic activity of hit candidates was similar to that of the drugs. The compounds demonstrated high intestinal absorption, and their total clearance rates were nearly the same as those of the reference drugs, indicating their potential suitability for use as drugs.

The comparative analysis of the pharmacokinetics and toxicity of the top compounds against reference drugs indicated their lower toxicity and potential to control diabetes. ADMET results recommended additional investigation of the hit molecules first through *in vitro* and and then through *in vivo* experimental trials to determine their suitability for human consumption.

Table 4. Drug-likeness and toxicity prediction of top three compounds along with reference drugs

ADMET parameters	Compounds				
	Copaborneol	**3-alpha-hydroxy-manool**	**Methyl 8-pimaren-18-oate**	**Miglitol**	**Voglibose**
Lipinski's rule (RO5)	Accepted	Accepted	Accepted	Accepted	Accepted
AMES toxicity	No	No	No	No	No
Hepatotoxicity	No	No	No	No	No
Skin Sensitisation	No	No	No	No	No
Genotoxicity	No	No	No	No	No
Cytotoxicity	No	No	No	No	No

ADMET parameters	Compounds				
	Copaborneol	**3-alpha-hydroxy-manool**	**Methyl 8-pimaren-18-oate**	**Miglitol**	**Voglibose**
BBB penetration	Yes	No	Yes	No	No
CYP2D6 substrate	No	No	No	No	No
CYP3A4 substrate	Yes	Yes	Yes	Yes	No
CYP1A2 inhibitor	Yes	Yes	No	No	No
CYP2C19 inhibitor	Yes	No	No	No	Yes
CYP2C9 inhibitor	No	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	No
CYP3A4 inhibitor	No	No	No	No	No
Intestinal absorption	High	High	High	Moderate	Low
Total Clearance (log ml/min/kg)	0.919	1.049	0.727	0.815	0.909

The GC-MS analysis of *L. lavandulifolia* oil demonstrated the presence of 28 compounds, with methyl 8-pimaren-18-oate being the most abundant (37.09%). Molecular docking revealed copaborneol, 3-alpha-hydroxy-manool, and methyl 8-pimaren-18-oate as top candidates, showing strong binding with the α-glucosidase enzyme, suggesting potential inhibition of the enzyme's normal function. The protein-ligand interactions demonstrated various hydrophobic and hydrophilic interactions with key amino acid residues, potentially disrupting α-glucosidase function. ADMET predictions showed these compounds have favorable pharmacokinetic and safety profiles, with low toxicity and good drug-likeness, highlighting their potential as anti-diabetic agents.

4. CONCLUSION

The present study identified 28 molecules from the oil of *L. lavandulifolia* using a GC-MS experiment. Among these compounds, copaborneol and 3-alpha-hydroxy-manool exhibited stronger binding with α-glucosidase than with the native ligand and reference drugs. The drug-likeness and toxicity assessment profiles depicted the drug-like properties of the hit candidates comparable to those of the reference drugs, suggesting potential use in diabetes management. However, for the validation of the computational results, additional *in vitro* and *in vivo* experiments are recommended.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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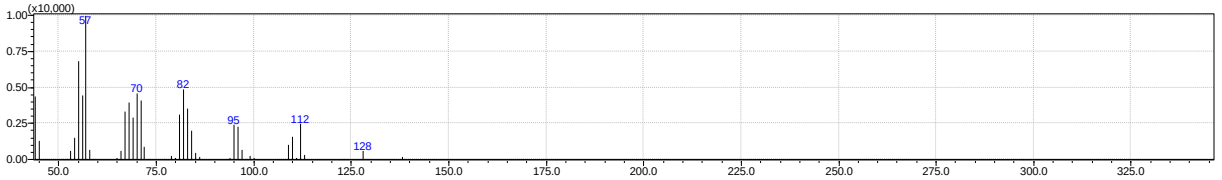
SUPPLEMENTARY INFORMATION



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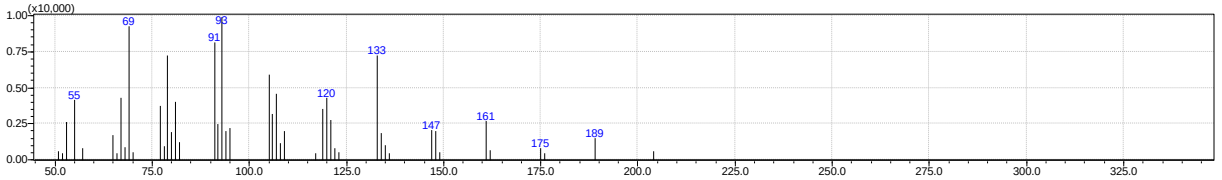

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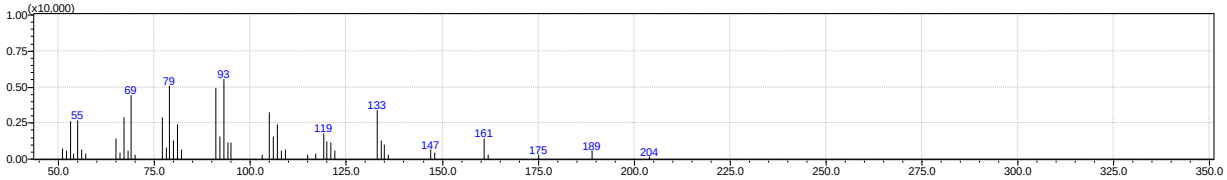

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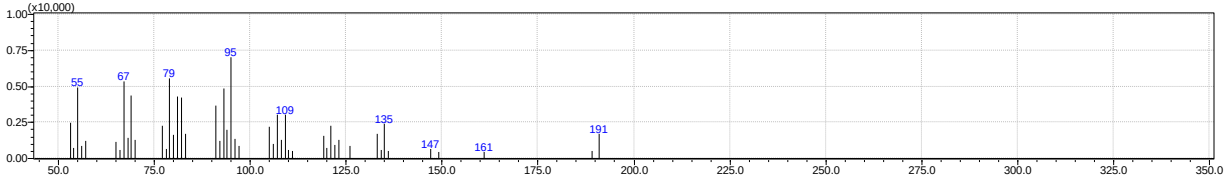

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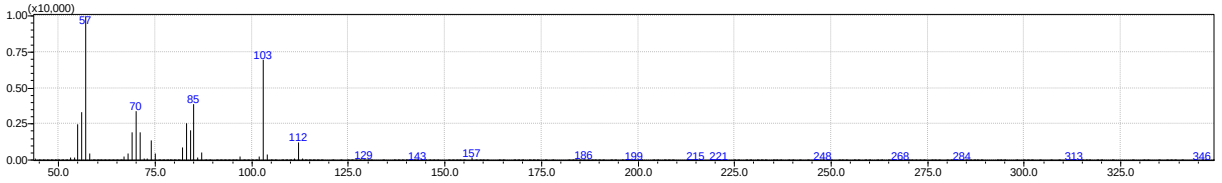

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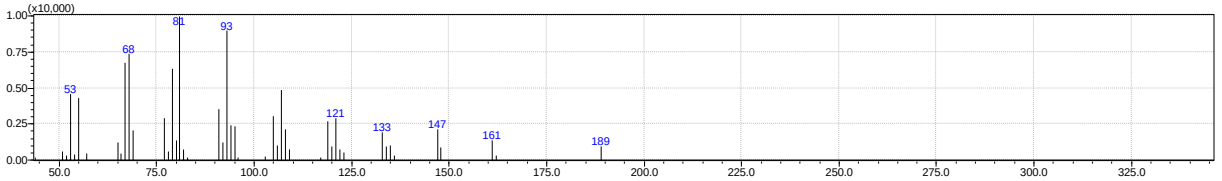

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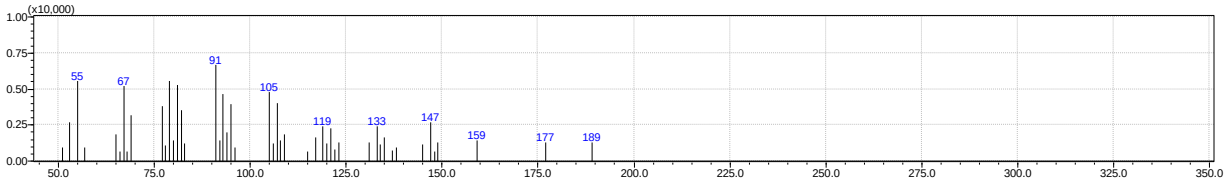

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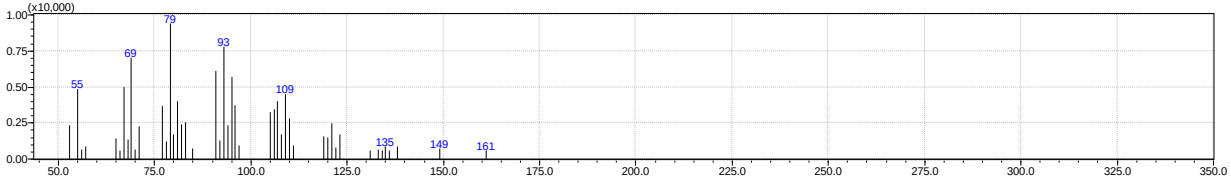

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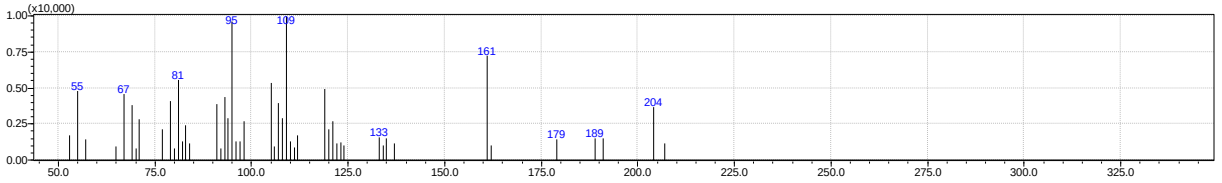

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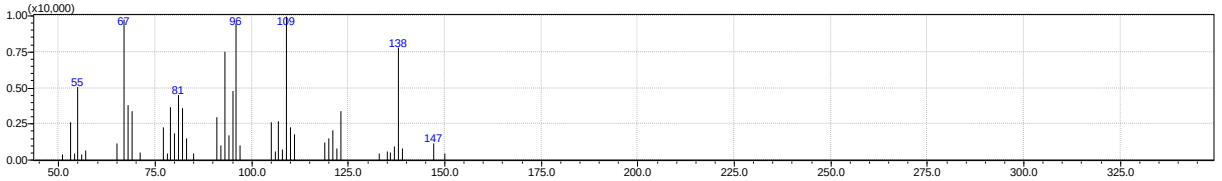

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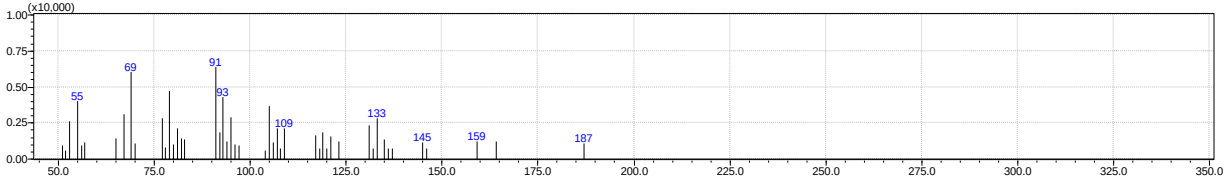

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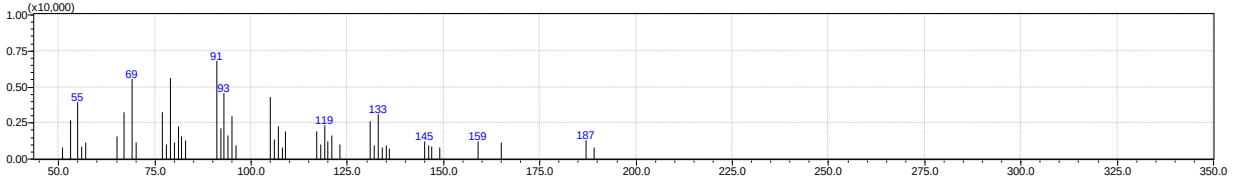
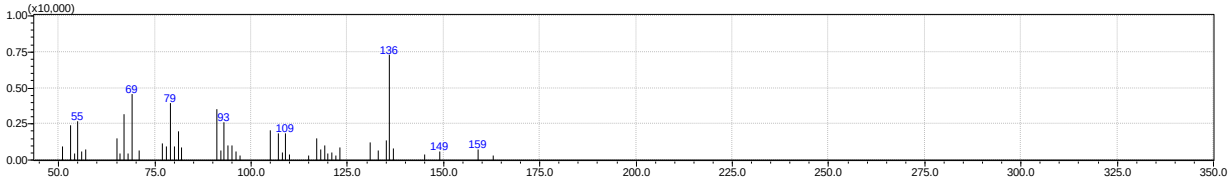
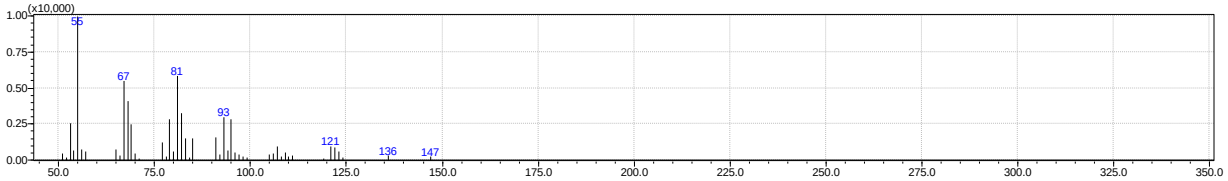


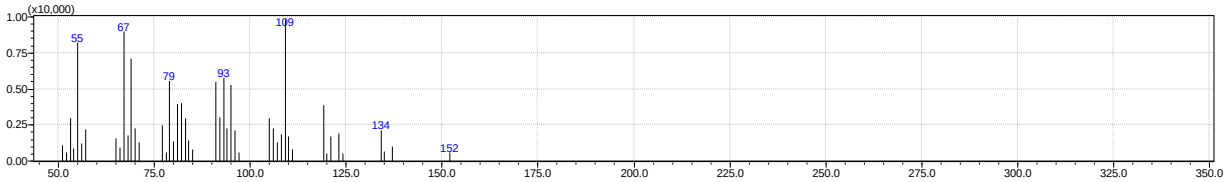
Caryophyllene <14-hydroxy-9-epi-(E)->



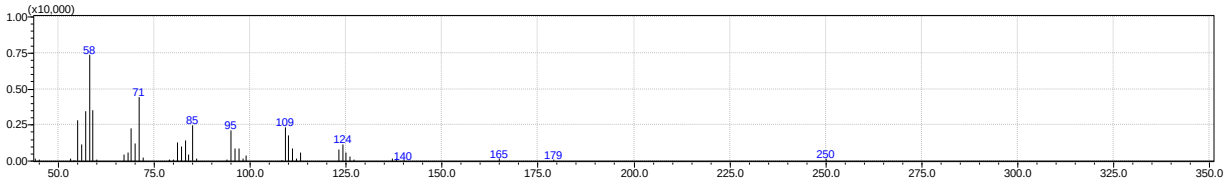
Caryophylla-4(12),8(13)-dien-5-alpha-ol



Deca-4,9-dienal <4,8-dimethyl-, trans->



Mentha-1(7),8-dien-2-ol <cis-, para->



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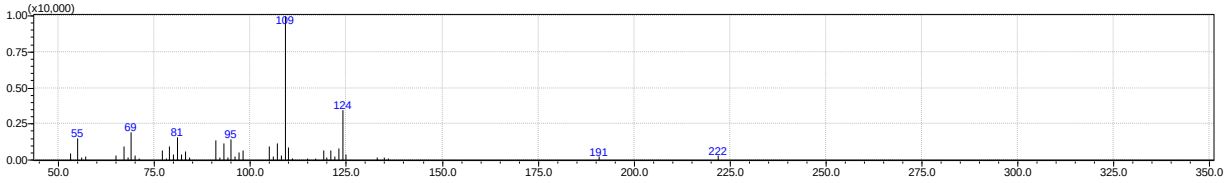
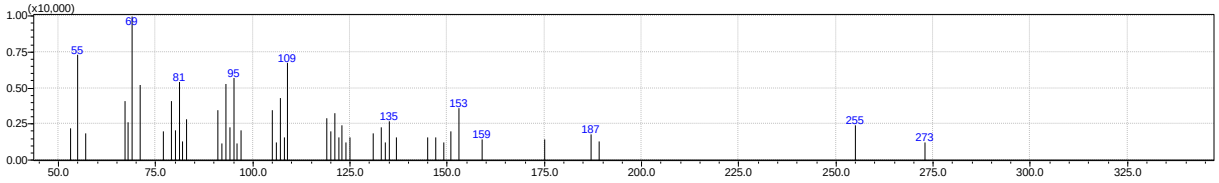
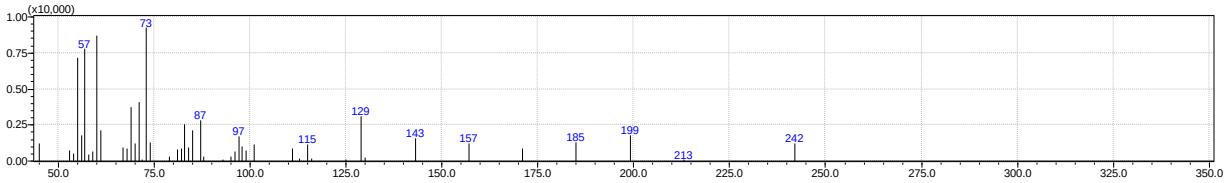


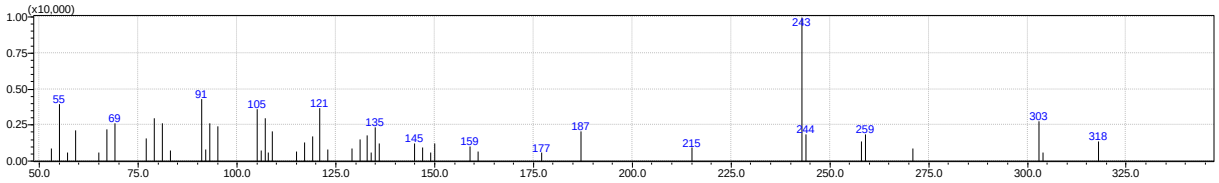
Drimenol



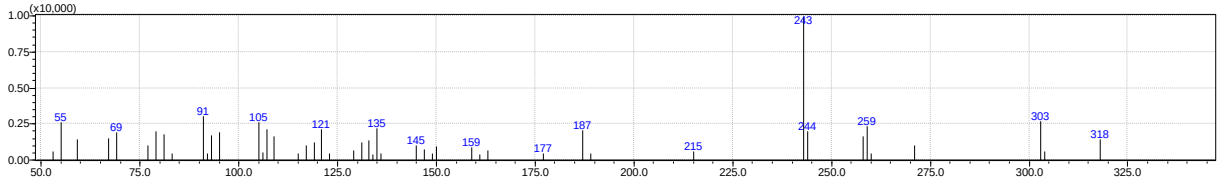
Larixol



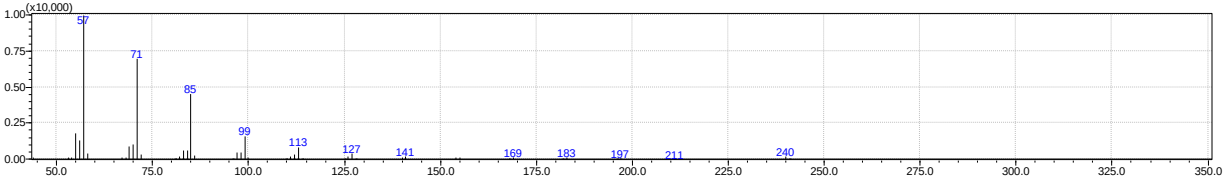
Pentadecylic acid



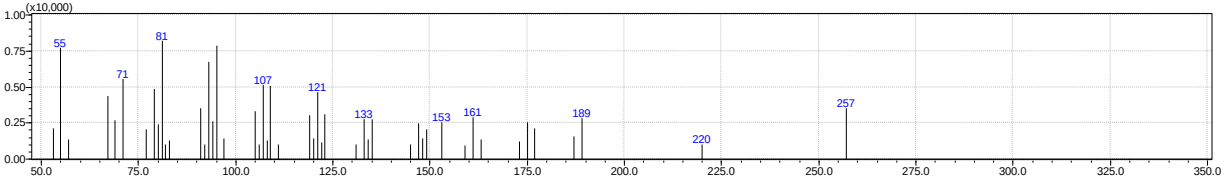
Valerianol



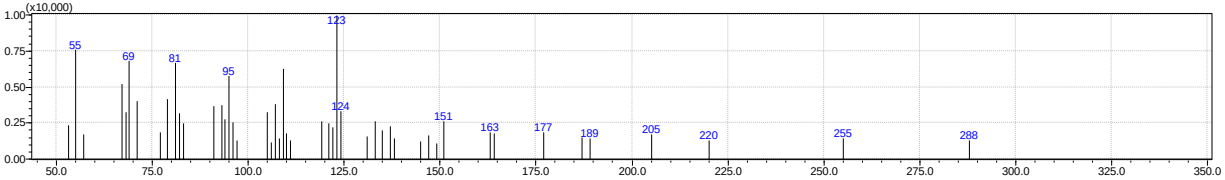
8-Piramen-18-oate <methyl->



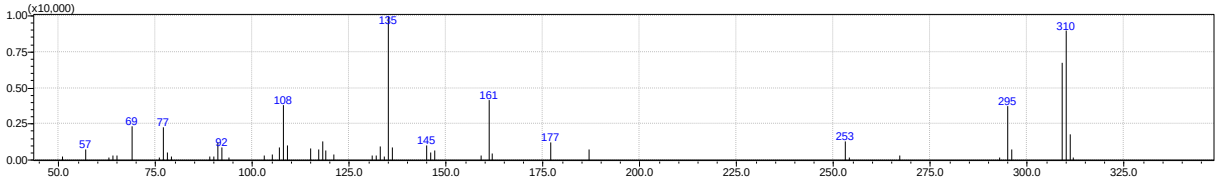
Heptadecane <n->



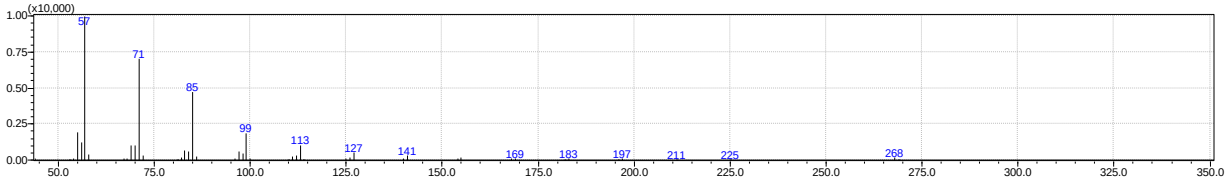
Torulosol



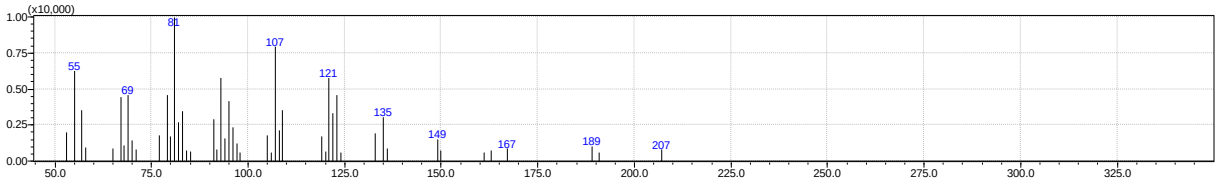
Manool <7-alpha-hydroxy->



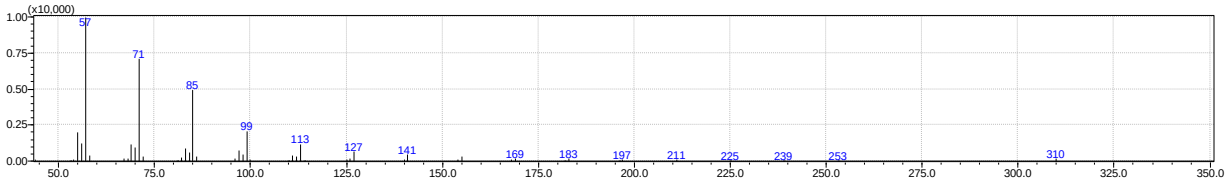
Avobenzone



Nonadecane <n->

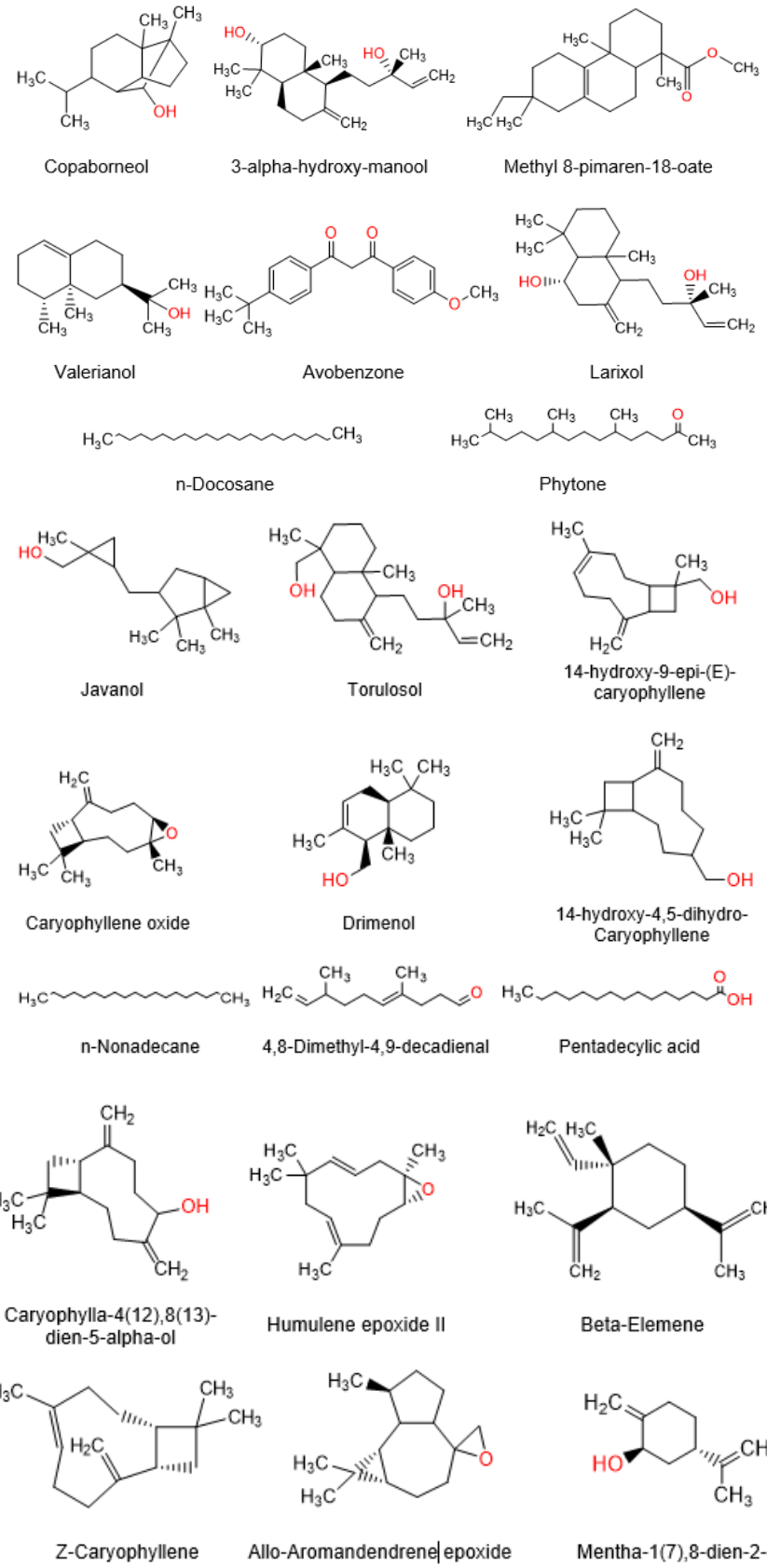


Javanol



Docosane <n->

Fig. S1. Mass spectra of compounds identified in the oil of *Leucas lavandulifolia* Sm.


Copaborneol
3-alpha-hydroxy-manool
Methyl 8-pimaren-18-oate
Valerianol
Avobenzone
Larixol
n-Docosane
Phytone
Javanol
Torulosol
14-hydroxy-9-epi-(E)-caryophyllene
Caryophyllene oxide
Drimenol
14-hydroxy-4,5-dihydro-Caryophyllene
n-Nonadecane
4,8-Dimethyl-4,9-decadienal
Pentadecylic acid
Caryophylla-4(12),8(13)-dien-5-alpha-ol
Humulene epoxide II
Beta-Elemene
Z-Caryophyllene
Allo-Aromandendrene epoxide
Mentha-1(7),8-dien-2-ol

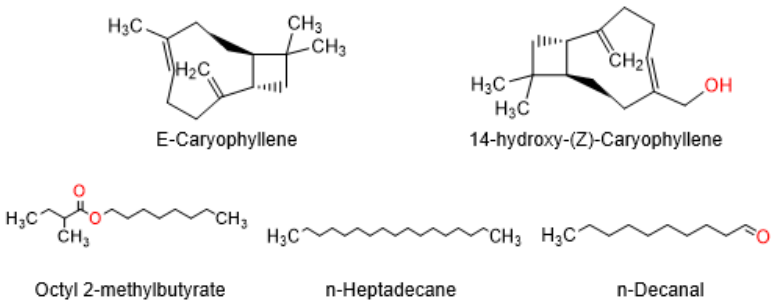


Fig. S2. Structures of compounds identified from the oil of *Leucas lavandulifolia* Sm.

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