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Anti-Obesity Potential of *Secamone afzelii* K. Leaf and Vine Ethanol Extract: Insights into Lipase Inhibition and Secondary Metabolites

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Abstract: Pancreatic lipase is an enzyme crucial for breaking down fats through hydrolysis, and inhibiting it is important for managing obesity. This study evaluated the lipase inhibitory profile of the leaf (SALE) and vine (SAVE) of *Secamone afzelii*, explored the modes of inhibition, identified the primary compounds responsible for this effect, and examined their molecular interactions with lipase using in vitro and in silico techniques. SALE (IC₅₀: 0.41 ± 0.02 mg/mL) exhibited higher lipase inhibitory activity compared to SAVE (IC₅₀: 0.95 ± 0.05 mg/mL), although it was significantly lower than orlistat (IC₅₀: 0.07 ± 0.00 mg/mL) across all concentrations. *S. afzelii* extracts inhibited lipase activity through an uncompetitive mode of inhibition. Gas chromatography-mass spectroscopy identified 54 and 47 compounds in SALE and SAVE, respectively, with 9,12-octadecadienoic acid (Z, Z)-, n-hexadecanoic acid and 4S,6R-dimethyl-7R-hydroxynonan-3-one identified as the most abundant compounds in both extracts. The binding energy of the top five ligands from *S. afzelii* ranged from −7.7 to −6.6 kcal/mol, outperforming that of orlistat (−4.4 kcal/mol). The ligands and orlistat had similar binding poses stabilised by hydrogen and π interactions with CYS299, SER301, CYS304, ASN425 and VAL426. These compounds were predicted to possess promising pharmacokinetic, lipophilic and hydrophilic properties. These results offer insights into the traditional use of *S. afzelii* for treating obesity and valuable information on potential drug candidates that can be optimised for combating this disease.

Keywords: pancreatic lipase; *Secamone afzelii*; gas chromatography–mass spectroscopy; mode of inhibition; in vitro and in silico



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1. Introduction

Obesity is characterised by abnormal fat deposition and accumulation in adipose tissues and organs as a result of excessive calorie intake [1]. Cardiovascular diseases, insulin resistance, type 2 diabetes, hypertension, metabolic derangement and numerous non-communicable diseases have been associated with the onset of obesity [2]. This disease is a widespread global health issue affecting over 2 billion adults and millions of young children [2]. Enzymes play a role in the pathophysiology of several diseases, making them therapeutic targets of inhibitors to truncate or diminish their catalytic activity for the clinical management of disease onset [3]. Human pancreatic lipase (HPL) is an enzyme that hydrolyses fats into monoglycerides and free fatty acids, which are easily absorbed, contributing to obesity [4]. HPL is exclusively produced by the pancreas and rapidly

released into the gastrointestinal tract via the pancreatic duct, where it performs its lipolytic function in the small intestine [5]. Inhibiting this enzyme within the intestine reduces lipid digestion and absorption from the bloodstream, preventing obesity. It is important to note that many research groups have relied on porcine pancreatic lipase (PPL) for screening and characterising lipase inhibitor, due to the amino acid sequence similarity of approximately 86% and the shared aspartate–histidine–serine catalytic triad between HPL and PPL. In addition, HPL was not commercially available for research purposes until after the pandemic [6]. Using drugs such as orlistat to inhibit lipase activity has long been a therapeutic approach for managing obesity and related disorders. However, side effects such as flatulence, steatorrhea, oily spotting, bloating and general discomfort are observed due to their potent inhibition of pancreatic enzymes [7]. Natural products that exhibit anti-lipase activity are of interest due to their diverse chemical structures and abundant bioactive phytochemicals [1]. The discovery of new enzyme inhibitors from medicinal plants and natural products holds promise for treating obesity-related disorders [8,9].

Many developing nations depend heavily on traditional medicine, particularly medicinal plants and natural products, to meet their healthcare needs. Factors such as the presence of bioactive plant compounds, affordability, accessibility and longstanding traditional usage contribute to the preference for traditional medicine over modern alternatives in these regions [10]. When integrated into diets, plant-based nutraceuticals and medicines are crucial in weight management and demonstrating anti-obesity activities through numerous mechanisms, such as the modulation of digestive and de novo fatty acid synthesis enzymes [11,12]. *Secamone afzelii* K., a member of the Asclepiadaceae family, is traditionally used in West Africa to manage numerous diseases and ailments [13]. Recent reports indicate that the regular administration of *S. afzelii* for 28 days reduces weight gains in both male and female rats [14,15]. Atoe and Co, in their study, show that *S. afzelii* reduced the occurrence of arteriosclerotic cardiovascular events in preeclampsia by decreasing low-density lipoprotein cholesterol and triglycerides [16]. Despite these findings, the literature on the anti-lipase activity and molecular inhibitory mechanism of *S. afzelii* is lacking, despite the renewed attention toward medicinal plants as remedies for obesity, which stems from both the increasing expense of synthetic drugs and the numerous side effects associated with them [17]. This study examined the pancreatic lipase inhibitory profile of *S. afzelii* leaf and vine. To further understand the inhibition property, we explored the mode of inhibition and reaction kinetics exerted by the leaf and vine on pancreatic lipase and identified the key compounds responsible for this inhibitory activity in these plant parts using gas chromatography–mass spectroscopy (GC-MS). In addition, an investigation of interactions between the identified phytochemicals and lipase was carried out to better understand the anti-lipase activity at a molecular level.

2. Materials and Methods

2.1. Chemicals and Reagents

Morpholinepropanesulphonic acid (MOPS), dimethyl formamide and p-nitrophenol were procured from Sigma Aldrich (Darmstadt, Germany), while porcine pancreatic lipase (EC 3.1.1.3, 99% HPLC, Cat.No L8070, CAS:9001-62-1), orlistat and p-nitrophenyl butyrate were obtained from Solarbio Life Science, Beijing, China. All remaining chemicals and reagents utilised were of analytical quality.

2.2. Collection of Plants, Identification and Preparation of Crude Extracts

Secamone afzelii, collected in March 2021 from Lagelu, Oyo State (7.2942° N, 4.0423° E), was identified by Dr. J. O. Popoola of the Biological Sciences Department at Covenant University, Ota, Ogun State, Nigeria, and assigned the identification number SA/CUBio/L013. The plant specimen was deposited in the herbarium. *S. afzelii* is not listed as a threatened species according to the International Union for Conservation of Nature. According to the method described by Iheagwam et al. [18], crude extracts of both the leaf (SALE) and vine (SAVE) of *S. afzelii* were prepared using 80% hydroethanol.

2.3. Assay for Inhibition of Lipase and Inhibitory Kinetics

The inhibitory activities of SALE and SAVE against porcine pancreatic lipase were assessed following a method slightly modified from Kim et al. [19]. In brief, an enzyme buffer was prepared by combining 30 μ L of a solution containing porcine pancreatic lipase (2.5 mg/mL in 10 mM MOPS and 1 mM EDTA, pH 6.8) with 850 μ L of Tris buffer (100 mM Tris-HCl and 5 mM CaCl_2 , pH 7). Subsequently, 100 μ L of extracts/orlistat (200–1000 μ g/mL) was added and incubated at 37 °C for 15 min. Ten microliters of substrate (10 mM p-NPB in dimethyl formamide) was then added and incubated at 37 °C for 30 min. Enzyme activity was determined by measuring p-nitrophenol release at 405 nm using an ELISA reader, and inhibition was calculated using Equation (1):

$$\% \text{ inhibition} = 100 \times \left(1 - \frac{B - b}{A - a} \right) \quad (1)$$

where A and B represent enzyme activity without and with inhibitor, respectively, and a and b represent negative controls without and with inhibitor, respectively. Experiments were replicated thrice.

Lipase activity was assessed using various concentrations of substrate p-NPB (0.2–1 mM) in the presence and absence of the extract (1000 μ g/mL) similar to the inhibition protocol followed to determine the inhibition mode. The Lineweaver–Burk plot was employed to calculate the Michaelis constant and maximal velocity.

2.4. Gas Chromatography–Mass Spectroscopy (GC-MS) Analysis

A GC–MSD 5975 Agilent instrument was used to assess the GC-MS analysis of SALE and SAVE, following the method described by Iheagwam et al. [20]. The GC conditions included pure helium as the carrier gas (linear velocity: 37 cm/s and flow rate: 1.56 mL/min), with the initial column oven temperature set at 60 °C, programmed to increase to 160 °C at a rate of 10 °C/min, and finally to 250 °C with a 2 min hold time per increment. The injection volume was 0.5 μ L in splitless mode with a split ratio of 1:1, and the injector temperature was maintained at 200 °C. For the mass spectrometer settings, the ion source temperature was 230 °C, and the interface temperature was 250 °C, with a solvent delay of 4.5 min. Mass spectra were acquired in the scan range of 50–700 amu, with electron ionisation mode set at 70 eV and a multiplier voltage of 1859 V. To identify compounds, the retention times, fragmentation patterns and mass spectral data of unknown components in the extracts were compared with those in the Wiley and National Institute of Standards and Technology (NIST) libraries.

2.5. In Silico Lipase Inhibition, Druglikeness and Pharmacokinetic Prediction

Protein retrieval and preparation involved retrieving the three-dimensional structures of human pancreatic lipase (PDB ID: IN8S) from the RCSB Protein Data Bank (<https://www.rcsb.org/> [accessed on 5 June 2024]), removing co-crystallised ligands and non-standard residues, adding hydrogen atoms and charges and performing energy minimisation on the structures using Chimera v1.17.3 [21]. To generate and prepare the ligand library, we obtained the three-dimensional structures of 74 compounds identified through the GC-MS analysis of SAVE and SALE from PubChem (<https://pubchem.ncbi.nlm.nih.gov/> [accessed on 5 June 2024]). Orlistat, serving as the reference clinical compound, was also included in the library. Thereafter, the protein and ligands were imported and converted to .pdbqt format. DoGSiteScorer was used to identify all the potential binding pockets on the surface of the lipase (Supplementary Figure S1), and thereafter, a blind docking procedure was conducted with AutoDock Vina in PyRx adhering to the parameters (centre: 37 \times 20 \times 84 and dimension: 51 \times 48 \times 90 points separated by 1 Å). The subsequent analysis and visualisation of the binding interactions between HPL and its top 5 binding ligands were carried out using Discovery Studio 2021 [20,22–24]. The predicted inhibition constant (pK_i) of docked ligands was calculated as previously reported [20]. Pharmacokinetic parameters and the absorption, distribution, metabolism and excretion (ADME) properties of the

top 5 lipase inhibitory ligands from the GC-MS-identified compound were predicted using the SwissADME online server [25].

2.6. Statistical Analyses

One-way analysis of variance (ANOVA) was performed on the data, followed by Duncan's post-test analysis to assess significance at a 5% probability level. Results were presented as mean \pm standard deviation (SD) from three (3) replicates, and IBM SPSS Statistics 23 (IBM Corp., New York, NY, USA) was employed to conduct these statistical procedures. The IC_{50} values, which denote the extract concentrations required to reduce enzyme activity by 50%, were determined using graphical methods facilitated by Microsoft Excel 2020 (Microsoft Corp., Washington, DC, USA).

3. Result and Discussion

Lipase Inhibition and Kinetics

The inhibition of pancreatic lipase activity by SALE and SAVE is illustrated in Figure 1, where both SALE and SAVE elicited a concentration-dependent inhibition pattern. Notably, SALE (IC_{50} : 0.41 ± 0.02 mg/mL) exhibited higher lipase inhibitory activity compared to SAVE (IC_{50} : 0.95 ± 0.05 mg/mL), although it was significantly lower than orlistat (IC_{50} : 0.07 ± 0.00 mg/mL) across all concentrations. The mild inhibition of pancreatic lipase by SALE and SAVE implies that *S. afzelii* could effectively mitigate obesity and its adverse effects, buttressing its ethnopharmacological use as a decoction against obesity and cardiovascular disease [26]. Moderate inhibitors of pancreatic lipase are preferred to those that induce the complete suppression of the activity, such as orlistat, as they prevent the symptoms associated with the build-up of lipids in the digestive tract, such as steatorrhea, oily spotting, distorted fat-soluble vitamins absorption and a significant drop in serum cholesterol concentrations [7,27]. Moreover, the reduced risk of oxidising unhydrolysed lipids and generating reactive oxygen is less unlikely with *S. afzelii* than with synthetic inhibitors due to phytochemicals with antioxidant activities [28]. Figure 2 presents the Lineweaver–Burk plot showing that *S. afzelii* extracts inhibited lipase activity through uncompetitive mode. SALE and SAVE decreased the V_{max} from 1.11×10^{-1} mM/min to 3.07×10^{-2} and 3.84×10^{-2} mM/min and K_m from 1.01 mM to 0.25 and 0.31 mM of the lipase (Table 1). The uncompetitive inhibitory effect of *S. afzelii* on pancreatic lipase activity is most notable under conditions of high substrate concentrations, with inhibitors forming an enzyme–substrate–inhibitor (ESI) complex when the extract constituents bind to the enzyme–substrate (ES) complex [18]. Unlike competitive inhibition where increasing [S] reduces the effect of the inhibitor, an [S] increase in uncompetitive inhibition increases the inhibitory activity of uncompetitive inhibitors due to increased [ES], making *S. afzelii* advantageous in managing obesity [20]. The findings of this study were corroborated by a study conducted on *Phyllanthus chamaepeuce* Ridl. extracts of different polarity in which the leaves exhibited better lipase inhibitory activity than the stem; however, both plant parts elicited a noncompetitive mode of inhibition [29]. Similarly, SAVE's inhibitory capacity on lipase was better than phytosynthesised selenium nanoparticle (SeNP)- and light stress-mediated in vitro callus cultures of *Caralluma tuberculata* extract [30].

Figure 3a,b depict chromatograms revealing the presence of diverse phytochemicals in *S. afzelii*, characterised by distinct retention times with 56 peaks identified in SALE and 51 in SAVE chromatograms. The spectral data show the presence of 54 and 47 compounds in SALE and SAVE, respectively, with 9,12-octadecadienoic acid (Z, Z)-, n-hexadecanoic acid and 4S,6R-dimethyl-7R-hydroxynonan-3-one identified as the most abundant compounds. Twenty-nine compounds were present in both SALE and SAVE (Tables 2 and 3). The majority of the compounds present belong to the fatty acid and fatty acid ester class, such as n-hexadecanoic acid, hexadecanoic acid, ethyl ester, hexanoic acid, pentadecyl ester and 17-octadecynoic acid, to mention a few. Due to their lipophilic nature and backbone structures, these compounds are possible lipase inhibitory compounds, making them preferential lipase substrates inducing a possible competitive or noncompetitive inhibition [31]. A study

on *Lagenaria siceraria* fruit attributed the lipase inhibitory activity to the presence of fatty acids and their esters [32], while 17-octadecynoic acid was identified in the bioactive fraction of *Homalium zeylanicum* that elicited hypocholesterolaemia properties in obese diabetic [33]. Amino-containing compounds such as 2-amino-8-[3-d-ribofuranosyl]imidazo[1,2-a]-s-triazin-4-one, 2-myristinoyl-glycinamide and guanosine present in *S. afzelii* have been reported in other plant parts to possess anti-obesity, hypolipidemic and anti-atherosclerosis activities, respectively [34–38]. The presence of phenolic compounds in SAVE and SALE, such as phytol, mequinol and catechol, suggests that the observed in vitro lipase inhibitory activity might also be ascribed to them, corroborated by studies reporting phenolic compounds modulating pancreatic lipase activity and altering lipid digestion and absorption by forming complexes [39–41]. These groups of compounds and other identified phytochemicals synergistically work to exert the observed pancreatic lipase inhibitory activities of SALE and SAVE. The similar mode of inhibitory action may result from the similar phytocontents present in both extracts.

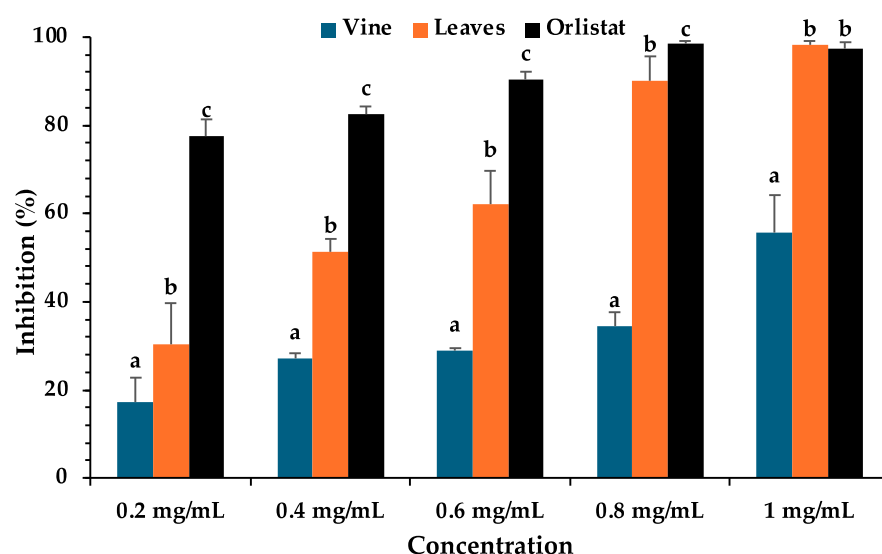


Figure 1. The inhibitory effect of *Secamone afzelii* leaf and vine extract on pancreatic lipase activity. Bars are expressed as mean \pm SD of triplicate determinations. Bars with different superscripts ^{a,b,c} on each concentration denote significant differences, while those with similar superscripts on each concentration are not significantly different ($p < 0.05$).

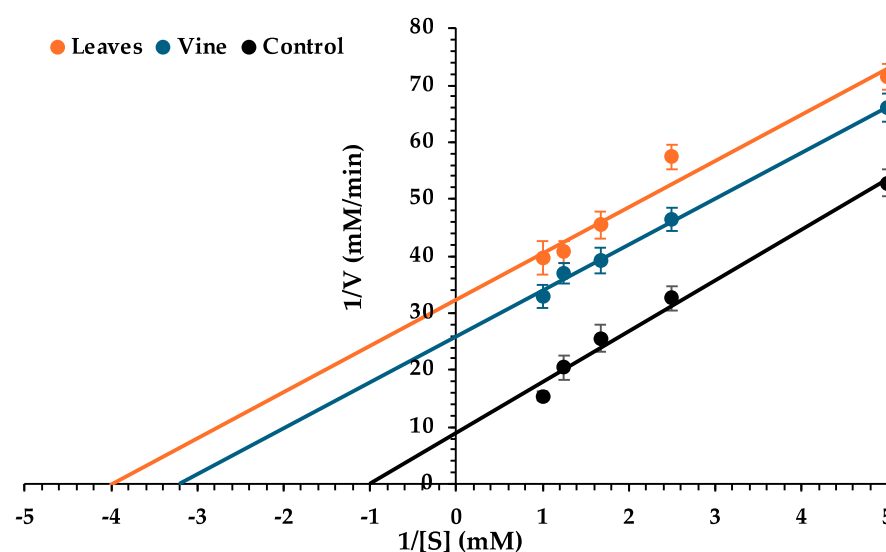
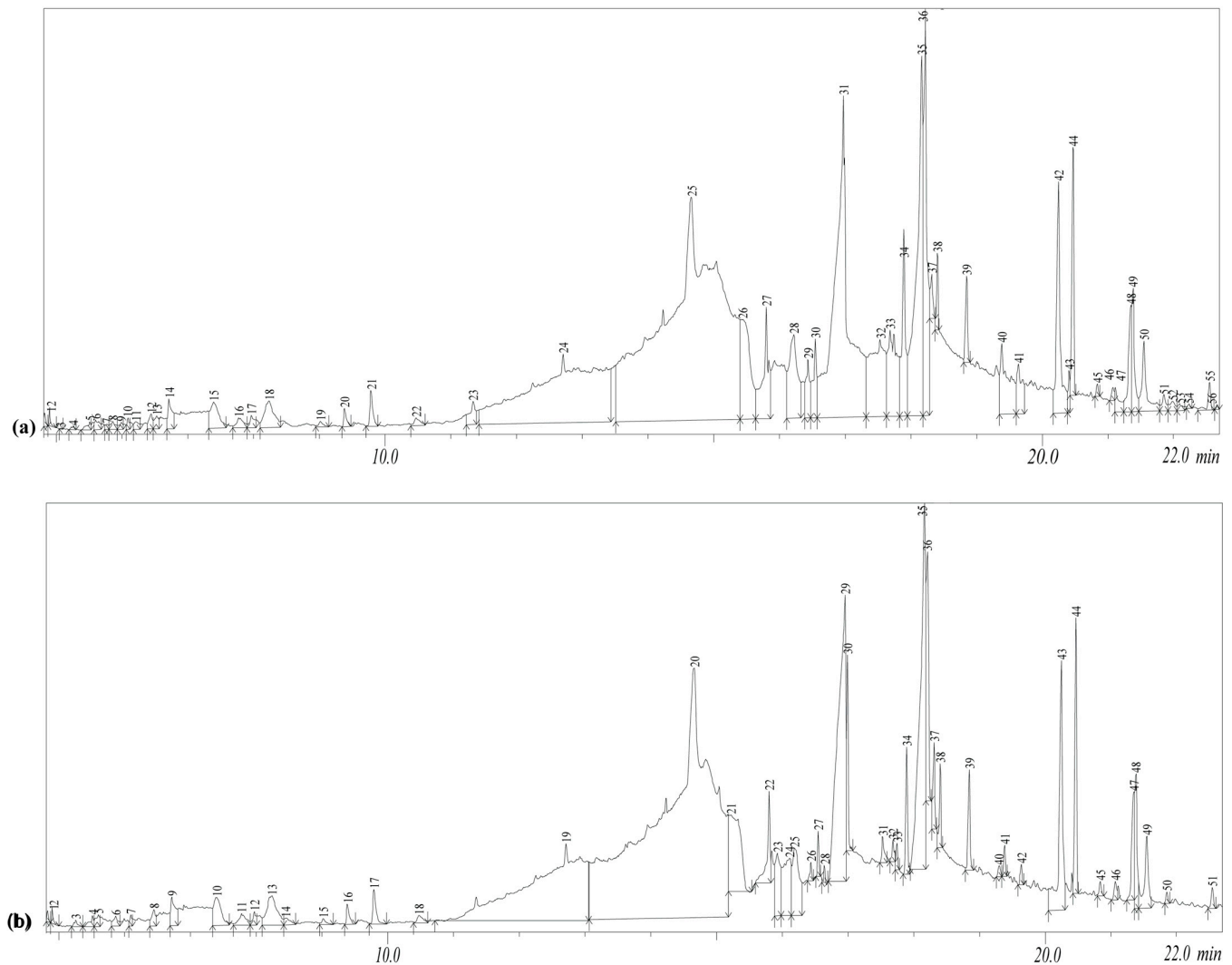


Figure 2. The mode of inhibition of *Secamone afzelii* leaf and vine extract on pancreatic lipase activity. Points are expressed as mean \pm SD of triplicate determinations.

Table 1. IC₅₀, V_{max}, and K_m values of *Secamone afzelii* leaf and vine extracts on pancreatic lipase activity.

	V _{max} (mM/min)	K _m (mM)	IC ₅₀ (mg/mL)
Leaves	3.07×10^{-2}	0.25	0.41 ± 0.02^b
Vine	3.84×10^{-2}	0.31	0.95 ± 0.04^c
No inhibitor	1.11×10^{-1}	1.01	—
Orlistat	—	—	0.07 ± 0.00^a

Data are represented as mean \pm SD of triplicate determinations. Values with different superscripts ^{abc} down the IC₅₀ column denote significant differences ($p < 0.05$). IC₅₀: half maximal inhibitory concentration; V_{max}: maximum velocity; K_m: Michaelis constant.

**Figure 3.** Gas chromatogram of *Secamone afzelii* ethanol (a) leaf and (b) vine extract.**Table 2.** Chemical constituents identified in *Secamone afzelii* leaf extract.

Peak No	Retention Number	Area %	Name	MW	Chemical Formula
1	4.819	0.06	Butane, 1,1'-oxybis[3-methyl-	158.28	C ₁₀ H ₂₂ O
2	4.891	0.08	Cyclohexanone	98.14	C ₆ H ₁₀ O
3	5.060	0.00	Cycloheptanol 2-chloro-, trans-	148.63	C ₇ H ₁₃ ClO
4	5.250	0.03	Cyclohexane, [2-[(2-ethylhexyl)oxy] ethyl]-	240.42	C ₁₆ H ₃₂ O
5	5.507	0.09	1,2,3-Thiadiazole-4-carboxylic acid, hydrazide	144.16	C ₃ H ₄ N ₄ OS
6	5.593	0.13	1,6-Anhydro-2,4-dideoxy-β-D-ribo-hexopyranose		C ₆ H ₁₀ O ₃
7	5.763	0.04	5-Hexen-2-ol, 5-methyl-	114.19	C ₇ H ₁₄ O
8	5.852	0.11	Pentanoic acid, 5-methoxy-, phenyl ester	208.25	C ₁₂ H ₁₆ O ₃

Table 2. Cont.

Peak No	Retention Number	Area %	Name	MW	Chemical Formula
9	5.982	0.08	Octane, 1-propoxy-	172.31	C ₁₁ H ₂₄ O
10	6.083	0.08	5.alpha.-Androstan-16-one, cyclic ethylene mercaptole	350.6	C ₂₁ H ₃₄ S ₂
11	6.210	0.10	Isosorbide Dinitrate	263.14	C ₆ H ₈ N ₂ O ₈
12	6.439	0.15	3-Allyloxy-1,2 propanediol	132.16	C ₆ H ₁₂ O ₃
13	6.524	0.16	2-Butanone, 4-hydroxy-3-methyl-	102.13	C ₅ H ₁₀ O ₂
14	6.710	0.35	Mequinol	124.14	C ₇ H ₈ O ₂
15	7.390	0.63	Erythritol	122.12	C ₄ H ₁₀ O ₄
16	7.767	0.20	Cyclopropane, 1-(1'-propenyl)-2 hydroxymethyl-	112.17	C ₇ H ₁₂ O
17	7.961	0.17	1-[2-Deoxy-.beta.-d-erythro-pento furanosyl] pyrrole-2,4-dicarboxamide	269.25	C ₁₁ H ₁₅ N ₃ O ₅
18	8.232	0.74	Catechol	110.11	C ₆ H ₆ O ₂
19	9.016	0.07	Hexanoic acid, pentadecyl ester	326.6	C ₂₁ H ₄₂ O ₂
20	9.382	0.15	2-Methoxy-4-vinylphenol	150.17	C ₉ H ₁₀ O ₂
21	9.785	0.32	Phenol, 2,6-dimethoxy-	154.16	C ₈ H ₁₀ O ₃
22	10.474	0.14	2-Amino-8-[3-dribofuranosyl]imidazo [1,2-a]-s-triazin-4-one	283.24	C ₁₀ H ₁₃ N ₅ O ₅
23	11.337	0.37	d-Mannitol, 1,4-anhydro-	164.16	C ₆ H ₁₂ O ₅
24	12.708	12.59	4S,6R-Dimethyl-7R-hydroxynonan-3-one	186.29	C ₁₁ H ₂₂ O ₂
25	14.661	34.33	Bicyclo[2.2.1.]hept-5-yl, methyl oxime	153.22	C ₉ H ₁₅ NO
26	15.433	2.79	1,3-Dioxane-5-methanol, 5-ethyl-	146.18	C ₇ H ₁₄ O ₃
27	15.799	1.71	2-Pentadecanone, 6,10,14-trimethyl-	268.5	C ₁₈ H ₃₆ O
28	16.216	2.06	1,2,3,4-Cyclohexanetetrol	148.16	C ₆ H ₁₂ O ₄
29	16.437	0.64	n-Decanoic acid	172.26	C ₁₀ H ₂₀ O ₂
30	16.550	0.76	1,2-Benzenedicarboxylic acid, butyl octyl ester	334.4	C ₂₀ H ₃₀ O ₄
31	16.978	11.97	n-Hexadecanoic acid	256.42	C ₁₆ H ₃₂ O ₂
32	17.537	3.35	n-Hexadecanoic acid	256.42	C ₁₆ H ₃₂ O ₂
33	17.687	2.23	Eicosanoic acid	312.5	C ₂₀ H ₄₀ O ₂
34	17.897	1.75	Phytol	296.5	C ₂₀ H ₄₀ O
35	18.165	6.05	9,12-Octadecadienoic acid (Z,Z)-	280.4	C ₁₈ H ₃₂ O ₂
36	18.223	4.04	6-Octadecenoic acid, (Z)-	282.5	C ₁₈ H ₃₄ O ₂
37	18.317	0.34	17-Octadecynoic acid	280.4	C ₁₈ H ₃₂ O ₂
38	18.403	0.34	Ethyl 14-methyl-hexadecanoate	298.5	C ₁₉ H ₃₈ O ₂
39	18.852	0.50	7-Hexadecenal, (Z)-	238.41	C ₁₆ H ₃₀ O
40	19.385	1.63	2H-Pyran-2-one, tetrahydro-6-tridecyl-	282.5	C ₁₈ H ₃₄ O ₂
41	19.643	0.78	Ethyl 9-hexadecenoate	282.5	C ₁₈ H ₃₄ O ₂
42	20.249	2.34	Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester	330.5	C ₁₉ H ₃₈ O ₄
43	20.411	0.23	Oxalic acid, mono-[5-[(2-bromophenyl) (2,2dimethylpropionyloxy)methyl]-7,8-dihydro-5H [1,3]dioxolo[4,5-g] isoquinolin-6-yl] ester		C ₂₄ H ₂₆ BrNO ₈
44	20.470	1.33	Bis(2-ethylhexyl) phthalate	390.6	C ₂₄ H ₃₈ O ₄
45	20.840	0.07	9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione	212.24	C ₁₁ H ₁₆ O ₄
46	21.073	0.10	Tetradecanoic acid,3,3a,4,6a,7,8,9,10, 10a,10b-decahydro-3a,10a-dihydroxy-5-(hydroxymethyl)- 2,10-dimethyl-3-oxobenz[e]azulen-8-yl ester, [3aR-(3a 2H-3,9a-Methano-1-benzoxepin, octahydro-2,2,5a,9-tetramethyl-, [3R-(3.alpha.,5a.alpha.,9.alpha.,9a.alpha.)]- 9,12-Octadecadienoic acid (Z, Z)-, 2,3-dihydroxypropyl ester	518.7	C ₃₁ H ₅₀ O ₆
47	21.115	0.31	9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester	222.37	C ₁₅ H ₂₆ O
48	21.352	0.94	Octadecanoic acid, 2,3-dihydroxypropyl ester	354.5	C ₂₁ H ₃₈ O ₄
49	21.381	0.95	8-Hexadecenal, 14-methyl-, (Z)-	356.5	C ₂₁ H ₄₀ O ₄
50	21.551	0.92	2-Myristinoyl-glycinamide	358.6	C ₂₁ H ₄₂ O ₄
51	21.855	0.19	i-Propyl 9-tetradecenoate	252.4	C ₁₇ H ₃₂ O
52	21.983	0.15	(E)-9-Octadecenoic acid ethyl ester	280.41	C ₁₆ H ₂₈ N ₂ O ₂
53	22.100	0.10	trans-Geranylgeraniol	268.4	C ₁₇ H ₃₂ O ₂
54	22.233	0.02	2H-3,9a-Methano-1-benzoxepin, octahydro-2,2,5a,9-tetramethyl-,	310.5	C ₂₀ H ₃₈ O ₂
55	22.549	0.21		290.5	C ₂₀ H ₃₄ O
56	22.663	0.03		222.37	C ₁₅ H ₂₆ O

MW: molecular weight.

Table 3. Chemical constituents identified in *Secamone afzelii* vine extract.

Peak No	Retention Time	Area %	Molecular Name	Molecular Weight	Chemical Formula
1	4.824	0.05	Butane, 1,1'-oxybis[3-methyl-	158.28	C ₁₀ H ₂₂ O
2	4.894	0.09	Cyclohexanone	98.14	C ₆ H ₁₀ O
3	5.252	0.07	Imidazole, 1,4,5-trimethyl-	110.16	C ₆ H ₁₀ N ₂
4	5.510	0.14	2-t-Butyl-4-methyl-5-oxo-[1,3]dioxolane-4-carboxylic acid	202.2	C ₉ H ₁₄ O ₅
5	5.597	0.17	1,6-Anhydro-2,4-dideoxy-.beta.-D-ribo-hexopyranose		C ₆ H ₁₀ O ₅
6	5.859	0.17	Benzenemethanamine, N,N-dimethyl-	135.21	C ₉ H ₁₃ N
7	6.087	0.10	1-Deoxy-d-mannitol	166.17	C ₆ H ₁₄ O ₅
8	6.441	0.21	3-Allyloxy-1,2 propanediol	132.16	C ₆ H ₁₂ O ₃
9	6.715	0.46	Mequinol	124.14	C ₇ H ₈ O ₂
10	7.396	0.74	Erythritol	122.12	C ₄ H ₁₀ O ₄
11	7.772	0.30	Glucosamine, N-acetyl-N-benzoyl-	325.31	C ₁₅ H ₁₉ NO ₇
12	7.966	0.16	Methyl salicylate	152.15	C ₈ H ₈ O ₃
13	8.235	1.04	Catechol	110.11	C ₆ H ₆ O ₂
14	8.444	0.15	2-Octanone, 1-nitro-	173.21	C ₈ H ₁₅ NO ₃
15	9.018	0.08	Hexanoic acid, pentadecyl ester	326.6	C ₂₁ H ₄₂ O ₂
16	9.386	0.20	2-Methoxy-4-vinylphenol	150.17	C ₉ H ₁₀ O ₂
17	9.790	0.39	Phenol, 2,6-dimethoxy-	154.16	C ₈ H ₁₀ O ₃
18	10.476	0.17	2-Amino-8-[3-d-ribofuranosyl]imidazo[1,2-a]-s-triazin-4-one	283.24	C ₁₀ H ₁₃ N ₅ O ₅
19	12.710	13.81	4S,6R-Dimethyl-7R-hydroxynonan-3-one	186.29	C ₁₁ H ₂₂ O ₂
20	14.663	43.52	4-((1E)-3-Hydroxy-1-propenyl)-2-methoxyphenol	180.2	C ₁₀ H ₁₂ O ₃
21	15.218	2.99	1,3-Dioxane-5-methanol, 5-ethyl-	146.18	C ₇ H ₁₄ O ₃
22	15.800	0.87	2-Pentadecanone, 6,10,14-trimethyl	268.5	C ₁₈ H ₃₆ O
23	15.925	1.11	d-Glycero-d-ido-heptose	210.18	C ₇ H ₁₄ O ₇
24	16.110	1.65	3-O-Methyl-d-glucose	194.18	C ₇ H ₁₄ O ₆
25	16.187	1.60	1,2,3,4-Cyclohexanetetrol	148.16	C ₆ H ₁₂ O ₄
26	16.439	0.14	Inositol, 1-deoxy-	164.16	C ₆ H ₁₂ O ₅
27	16.550	0.21	1,2- Benzenedicarboxylic acid, butyl octyl ester	334.4	C ₂₀ H ₃₀ O ₄
28	16.644	0.07	Guanosine	283.24	C ₁₀ H ₁₃ N ₅ O ₅
29	16.957	7.74	n-Hexadecanoic acid	256.42	C ₁₆ H ₃₂ O ₂
30	16.992	0.92	Hexadecanoic acid, ethyl ester	284.5	C ₁₈ H ₃₆ O ₂
31	17.529	0.25	n-Hexadecanoic acid	256.42	C ₁₆ H ₃₂ O ₂
32	17.684	0.15	9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione	212.24	C ₁₁ H ₁₆ O ₄
33	17.747	0.14	9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione	212.24	C ₁₁ H ₁₆ O ₄
34	17.891	0.77	Phytol	296.5	C ₂₀ H ₄₀ O
35	18.164	6.83	9,12-Octadecadienoic acid (Z,Z)-		C ₁₈ H ₃₂ O ₂
36	18.206	2.18	13-Tetradecenal	210.36	C ₁₄ H ₂₆ O
37	18.308	0.59	Octadecanoic acid	284.5	C ₁₈ H ₃₆ O ₂
38	18.402	0.47	Ethyl 14-methyl-hexadecanoate	298.5	C ₁₉ H ₃₈ O ₂
39	18.848	0.67	7-Hexadecenal, (Z)-	238.41	C ₁₆ H ₃₀ O
40	19.297	0.11	9-Octadecenal, (Z)-	266.5	C ₁₈ H ₃₄ O
41	19.381	0.18	2H-Pyran-2-one, tetrahydro-6-tridecyl-	282.5	C ₁₈ H ₃₄ O ₂
42	19.640	0.14	9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione	212.24	C ₁₁ H ₁₆ O ₄
43	20.248	2.96	Hexadecanoic acid, 2-hydroxy-1-(hydroxymethyl)ethyl ester	330.5	C ₁₉ H ₃₈ O ₄
44	20.468	1.66	Bis(2-ethylhexyl) phthalate	390.6	C ₂₄ H ₃₈ O ₄
45	20.840	0.11	9,9-Dimethoxybicyclo[3.3.1]nona-2,4-dione	212.24	C ₁₁ H ₁₆ O ₄
46	21.067	0.17	8-Heptadecene, 1-chloro-	272.9	C ₁₇ H ₃₃ Cl
47	21.352	1.03	9,12-Octadecadienoic acid (Z, Z)-, 2,3-dihydroxypropyl ester	354.5	C ₂₁ H ₃₈ O ₄
48	21.380	1.09	9-Octadecenoic acid (Z)-, 2hydroxy -1-(hydroxymethyl)ethyl ester	356.5	C ₂₁ H ₄₀ O ₄
49	21.546	0.98	Octadecanoic acid, 2,3-dihydroxy propyl ester	358.6	C ₂₁ H ₄₂ O ₄
50	21.852	0.07	8-Hexadecenal, 14-methyl-, (Z)-	252.4	C ₁₇ H ₃₂ O
51	22.543	0.16	2,6,10,14,18-Pentamethyl 2,6,10, 14,18-eicosapentaene	342.6	C ₂₅ H ₄₂

Molecular docking provides deeper insights into the binding interactions, strength and affinity between small molecule inhibitors and macromolecules [42]. The binding energy of the top five ligands from *S. afzelii* ranged from -7.7 to -6.6 kcal/mol, outperforming that of orlistat (-4.4 kcal/mol) with 5α -Androstan-16-one, cyclic ethylene mercaptol recording the lowest with a score of -7.7 kcal/mol (Table 4). The predicted inhibitory constants of the top five ligands were in consonance with the docking scores (Table 4). Twenty-eight other ligands recorded better binding scores and predicted inhibitory constants than orlistat, while five others had similar values, as shown in Supplemental Table S1. The low binding energy of the phytocompounds in *S. afzelii* compared to orlistat may be attributed to the hydrophobic nature of the backbone structures of these ligands and the higher number of hydrogen interactions stabilising these compounds in lipase, which contrasts with a report

where the number of hydrogen bonds did not affect docking scores [43]. Likewise, the low predicted inhibitory constant of the ligands indicates stable affinity, implying that only a small concentration of the ligands is required for enzyme inhibition [44]. All ligands and orlistat were stabilised by hydrogen and π bonds bar oxalic acid, mono-[5-[(2-bromophenyl)(2,2-dimethylpropionyloxy) methyl]-7,8-dihydro-5H[1,3] dioxolo [4,5-g]isoquinolin-6-yl} ester, which was stabilised by only π bonds. 5 α -Androstan-16-one, cyclic ethylene mercaptol and oxalic acid, mono-[5-[(2-bromophenyl) (2,2-dimethylpropionyloxy) methyl] -7,8-dihydro-5H [1,3] dioxolo [4,5-g] isoquinolin-6-yl} ester both formed π interactions with ARG111 (Figure 4a,d). 2-Amino-8-[3-d-ribofuranosyl]imidazo[1,2-a]-s-triazin-4-one and guanosine formed hydrogen bonds with CYS299, SER301, CYS304 and VAL426, while orlistat formed π bonds with these amino acid residues. However, 2-Amino-8-[3-d-ribofuranosyl] imidazo [1,2-a]-s-triazin-4-one and orlistat both formed hydrogen interactions with ASN425 (Figure 4b,c,f). 1-[2-Deoxy- β -d-erythro-pentofuranosyl]pyrrole-2,4-dicarboxamide was unique among the ligands in that it did not interact with any amino acid residues that interacted with the other top ligands or orlistat. (Figure 4e). The top five compounds with a low binding score and orlistat were stabilised by similar amino acid residues, which may suggest preferential binding to the ES complex compared to the free enzyme, to enact their lipase inhibitory effect, buttressing the in vitro findings. The high number of hydrogen interactions between the ligands and lipase could be attributed to CYS299, SER301, CYS304 and ASN425 amino acid residues. These amino acids are classified as polar amino acids and contain functional groups capable of forming hydrogen bonds with ligands [45]. Reports have shown these amino acid residues play a role in stabilising ligands in lipase [30,46,47].

Table 4. Binding affinity scores of the top five compounds to lipase.

SN	Compound	Binding Energy (kcal/mol)	pK _i (μ M)
1.	5 α -Androstan-16-one, cyclic ethylene mercaptol	−7.7	2.31×10^{-6}
2.	2-Amino-8-[3-d-ribofuranosyl]imidazo[1,2-a]-s-triazin-4-one	−6.9	8.89×10^{-6}
3.	Guanosine	−6.8	1.05×10^{-5}
4.	Oxalic acid, mono-[5-[(2-bromophenyl)(2,2-dimethylpropionyloxy) methyl]-7,8-dihydro-5H[1,3] dioxolo[4,5-g]isoquinolin-6-yl} ester	−6.7	1.24×10^{-5}
5.	1-[2-Deoxy-.beta.-d-erythro-pentofuranosyl]pyrrole-2,4-dicarboxamide	−6.6	1.47×10^{-5}
6.	Orlistat	−4.8	3.06×10^{-4}

pK_i: predicted inhibitory constant.

The in silico prediction of ADME properties is a rapid and efficient method in lead development that identifies potential failures in the course of drug development [48]. Figure 5 illustrates the pharmacokinetic properties of the top five ligands and orlistat. All compounds were predicted to be impermeable to the blood–brain barrier (BBB) and possess limited human intestinal absorption (HIA), except 5 α -androstan-16-one, cyclic ethylene mercaptol and oxalic acid, mono-[5-[(2-bromophenyl)(2,2-dimethylpropionyloxy) methyl]-7,8-dihydro-5H[1,3] dioxolo[4,5-g]isoquinolin-6-yl} ester, which were predicted to be passively absorbed in the human intestine. Similarly, none of the ligands were predicted to be P-glycoprotein (P-gp) substrates except oxalic acid, mono-[5-[(2-bromophenyl)(2,2-dimethylpropionyloxy) methyl]-7,8-dihydro-5H[1,3] dioxolo[4,5-g]isoquinolin-6-yl} ester (Figure 5). All ligands that were not predicted to be P-gp substrates have a high probability of being bioavailable and effective without any change in their ADME properties [44]. This is due to P-gp's role as an ATP-dependent protein that confers protection by actively transporting exogenous molecules, preventing intracellular concentration [49].

None of the top five lipase inhibitory ligands were predicted inhibitors of any cytochrome P₄₅₀ (CYP₄₅₀) enzyme isoform, violators of Lipinski's rule of five (RO5) and pan-assay interference compounds (PAINSs). They were also predicted to possess favourable availability and synthetic accessibility scores with low skin permeability scores. However, 5 α -androstan-16-one, cyclic ethylene mercaptol was predicted to inhibit three CYP₄₅₀ isoforms (1A2, 2C19 and 2C29) and violate one RO5 (MLOGP > 4.15), while oxalic

acid, mono-[5-[(2-bromophenyl)(2,2-dimethylpropionyloxy) methyl]-7,8-dihydro-5H[1,3] dioxolo[4,5-g]isoquinolin-6-yl] ester violated one RO5 (MW > 500) as well (Table 5). Structure-based drug design addresses challenges encountered during the design of pharmaceuticals, and adherence to RO5 criteria is crucial to prevent failures during clinical trials [20,50]. Compounds are anticipated to possess favourable pharmacokinetic properties if they satisfy RO5 criteria with one or no violation [42]. The accumulation of drugs and decreased drug metabolism are the effects of CYP₄₅₀ inhibition, which may result in enhanced pharmacological effects or clinical toxicity [51]. PAINs are compounds with misleading positive outcomes and nonspecific interactions with various biological targets rather than being specific due to disruptive functional groups [52]. The top five lipase inhibitory ligands from *S. afzelii* are expected to exhibit good pharmacokinetic characteristics, be specific in inhibiting lipase activity and easily synthesised and integrated into a complex lead due to their chemical moieties and fragmental contribution [25].

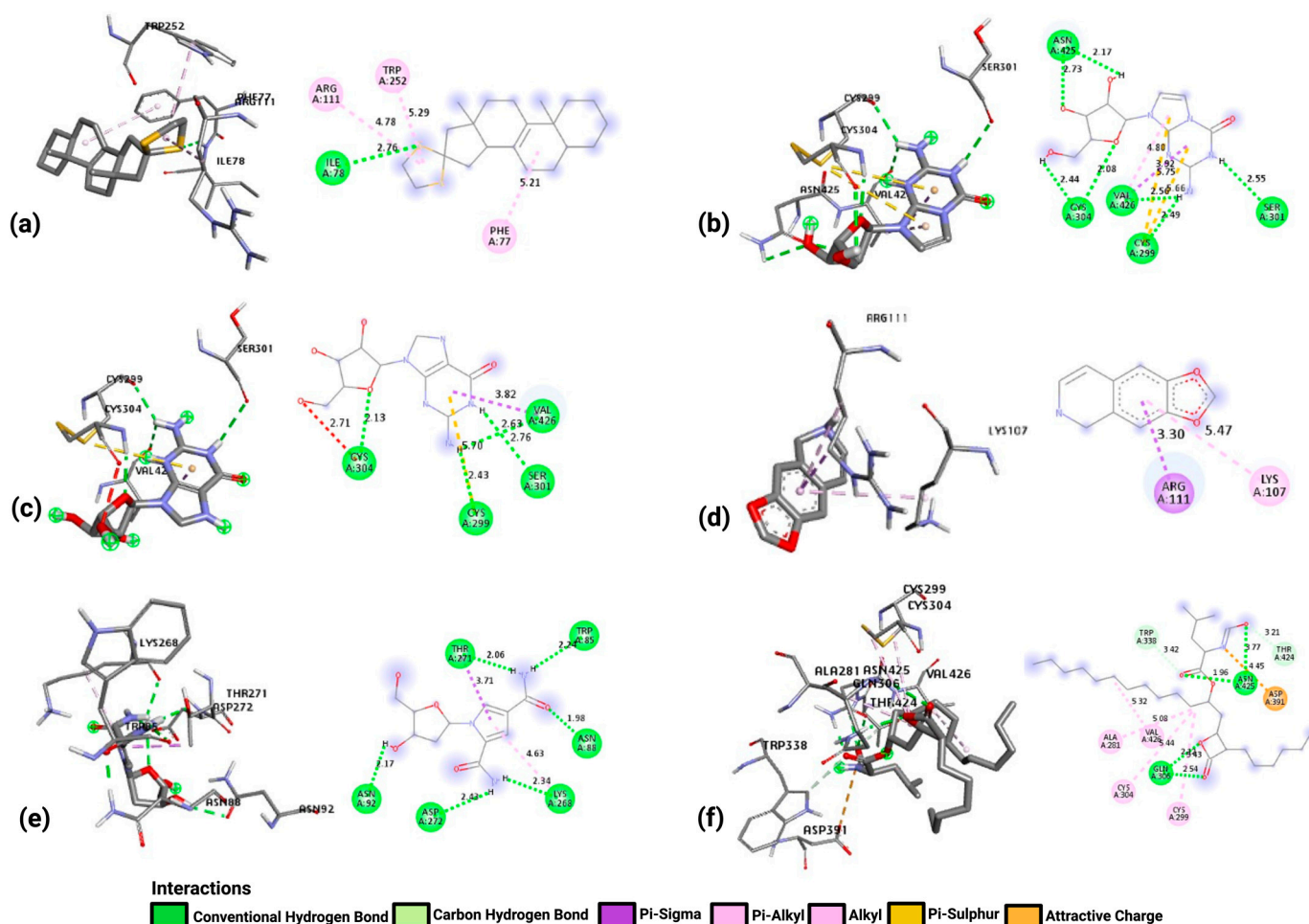


Figure 4. Binding interaction pose between (a) 5 α -Androstan-16-one, cyclic ethylene mercaptole, (b) 2-Amino-8-[3-d-ribofuranosyl]imidazo[1,2-a]-s-triazin-4-one, (c) guanosine, (d) oxalic acid, mono-[5-[(2-bromophenyl)(2,2-dimethylpropionyloxy) methyl]-7,8-dihydro-5H-[1,3]dioxolo[4,5-g]isoquinolin-6-yl] ester, (e) 1-[2-Deoxy-.beta.-d-erythropento furanosyl]pyrrole-2,4-dicarboxamide, and (f) orlistat with lipase.

Lipophilicity and hydrophilicity are critical factors influencing the absorption and distribution of pharmaceutical compounds, as the lipophilicity of a drug promotes efficient lipid bilayer penetration while the handling and formulation depend on hydrophilicity. When these solubility properties are not in an optimal ratio, such as a drug with high lipophilic and hydrophobic properties, it tends to accumulate in the body, due to poor excretion, and potentially increase toxicity [46]. 5 α -Androstan-16-one, cyclic ethylene

mercaptole had a predicted Consensus LogP of 6.05, while the other compounds recorded values of 0.08 to −2.23. Likewise, the respective predicted ESOL and Ali LogS values of 5 α -androstan-16-one, cyclic ethylene mercaptole were −6.9 and −8.67, while the other compounds recorded values of −4.73 to −0.04 and −5.23 to 0.23, respectively (Figure 6). Consensus LogP is the arithmetic mean of the five predicted partition coefficient between n-octanol and water values to measure lipophilicity; hence, the higher the value, the higher the lipophilic nature [25]. ESOL and Ali LogS are measures of compound solubility in water with a range of −12 to 1, and the levels of solubility can be classified as insoluble < −10 poorly < −6 moderately < −4 soluble < −2 very < 0 < highly [53,54]. This suggests that all compounds except 5 α -androstan-16-one, cyclic ethylene mercaptole showed a good balance of lipophilicity and hydrophilicity ratio, suggesting favourable properties to exert their lipase inhibitory effect and be excreted, preventing unwanted accumulation. The aforementioned exception is highly lipophilic and insoluble in water.

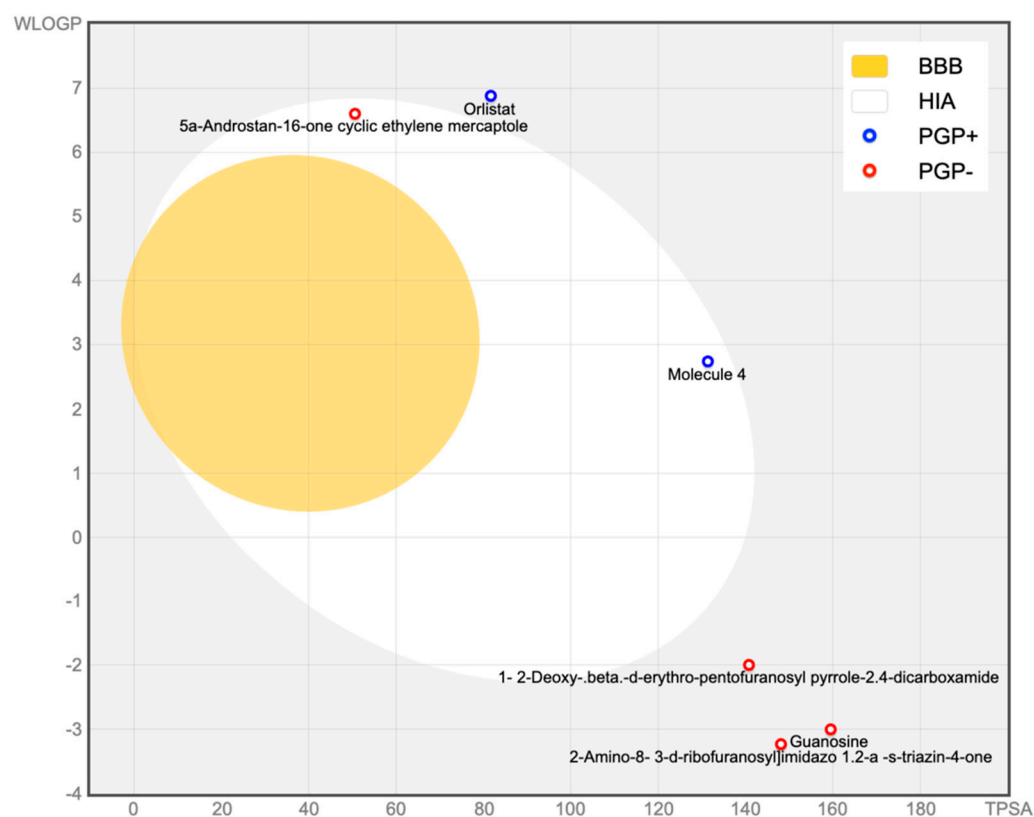


Figure 5. Pharmacokinetic characteristics of top five lipase inhibitory ligands from *Secamone afzelii* illustrated with BOILED–egg graph. Molecule 4: oxalic acid, mono-[5-[(2-bromophenyl)(2,2-dimethylpropionyloxy) methyl]-7,8-dihydro-5H[1,3] dioxolo[4,5-g]isoquinolin-6-yl] ester.

Table 5. ADME prediction of top five lipase inhibitory ligands from *Secamone afzelii*.

Mol No	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	log Kp (cm/s)	Lipinski	PAINS	BA	SA
1	Yes	Yes	Yes	No	No	−2.93	1	-	0.55	6.1
2	No	No	No	No	No	−10.01	-	-	0.55	3.86
3	No	No	No	No	No	−9.37	-	-	0.55	3.86
4	No	No	No	No	No	−7.51	1	-	0.55	4.7
5	No	No	No	No	No	−9.28	-	-	0.55	3.6

Mol 1: 5 α -Androstan-16-one, cyclic ethylene mercaptole, Mol 2: 2-Amino-8-[3-d-ribofuranosyl]imidazo[1,2-a]-s-triazin-4-one, Mol 3: guanosine, Mol 4: oxalic acid, mono-[5-[(2-bromophenyl)(2,2-dimethylpropionyloxy) methyl]-7,8-dihydro-5H[1,3] dioxolo[4,5-g]isoquinolin-6-yl] ester, Mol 5: 1-[2-Deoxy-.beta.-d-erythro-pentofuranosyl]pyrrole-2,4-dicarboxamide, BA: bioavailability scores, SA: synthetic accessibility.

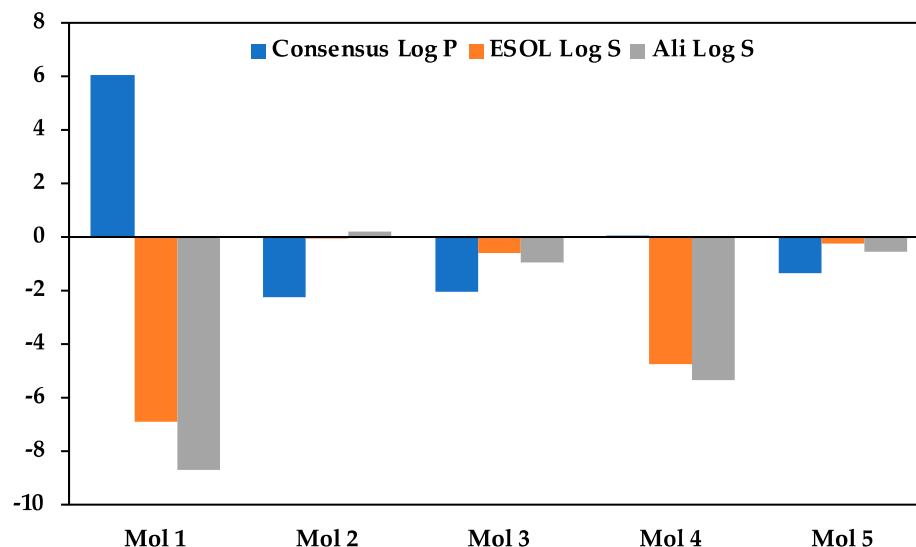


Figure 6. Predicted lipophilicity and hydrophilicity values of top five lipase inhibitory ligands from *Secamone afzelii*. Mol 1: 5 α -Androstan-16-one, cyclic ethylene mercaptole, Mol 2: 2-Amino-8-[3-d-ribofuranosyl]imidazo[1,2-a]-s-triazin-4-one, Mol 3: guanosine, Mol 4: oxalic acid, mono-{5-[(2-bromophenyl)(2,2-dimethylpropionyloxy) methyl]-7,8-dihydro-5H[1,3] dioxolo[4,5-g]isoquinolin-6-yl} ester, Mol 5: 1-[2-Deoxy-.beta.-d-erythro-pentofuranosyl] pyrrole-2,4-dicarboxamide.

4. Conclusions

In this study, *S. afzelii* demonstrated a notable inhibitory effect on pancreatic lipase activity through uncompetitive mechanisms, as confirmed by computational studies. This activity can be attributed to a plethora of phytochemicals present in the leaves and the vines of which 5 α -androstan-16-one, cyclic ethylene mercaptole, 2-amino-8-[3-d-ribofuranosyl]imidazo[1,2-a]-s-triazin-4-one, guanosine, oxalic acid, mono-{5-[(2-bromophenyl)(2,2-dimethylpropionyloxy) methyl]-7,8-dihydro-5H[1,3]dioxolo[4,5-g]isoquinolin-6-yl} ester and 1-[2-Deoxy-.beta.-d-erythro-pentofuranosyl]pyrrole-2,4-dicarboxamide are the major principles responsible for the anti-lipase property. These compounds were predicted to possess pharmacokinetic, lipophilic and hydrophilic properties required to become promising leads that can be developed against lipase. However, functional groups can be added to 5 α -androstan-16-one, cyclic ethylene mercaptole and oxalic acid, mono-{5-[(2-bromophenyl)(2,2-dimethylpropionyloxy) methyl]-7,8-dihydro-5H[1,3]dioxolo[4,5-g]isoquinolin-6-yl} ester to improve their solubility ratio and P-glycoprotein substrate status, respectively. These results offer insights into the traditional use of *S. afzelii* for treating obesity, along with valuable information on potential drug candidates that can be optimised for combating obesity. Therefore, *S. afzelii* emerges as a promising candidate for exploration as a natural alternative treatment for managing this disease. This study's limitation includes the inability to isolate the potent bioactive compounds identified in silico responsible for their anti-lipase effect, and this necessitates further research in addition to an in vivo validation of the anti-lipase potential of *S. afzelii*.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/sci6040070/s1>, Figure S1: Ligand-binding cavities of human pancreatic lipase predicted by DogSiteScorer; Table S1: The docking scores between SALE and SAVE ligands and human pancreatic lipase.

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