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Evaluation of hypolipidemic potentials of phytoconstituents in *Cymbopogon citratus* and *Piper guineense*: A Computational Approach

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ABSTRACT

***Background*:** Hyperlipidemia causes atherosclerotic cardiovascular disease, which constitutes one of the most common cardiovascular risk factors globally. The adverse effects and cost-effectiveness of hypolipidemic drugs, as well as the safety of herbs, remain a major challenge. Consequently, the hypolipidemic potential and toxicity profile of phytoconstituents in *Cymbopogon citratus* and *Piper guineense* were evaluated using a computational approach.

***Methods*:** Molecular docking was performed using Maestro 12.8, while SwissADME and ProTox-II were used to assess the drug-likeness and toxicity profiles of the phytoconstituents. The chemical structures of the phytoconstituents were docked against four key protein targets implicated in hyperlipidemia. The protein targets were 3-Hydroxy-3-methylglutaryl-coenzyme A Reductase (HMG-CoA Reductase, PDB ID 1HWK), Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ, PDB ID 6ENQ), Niemann-Pick C1-Like 1 (NCP1L1, PDB ID 7WGN), and Hydroxycarboxylic Acid Receptor 2 (HM7A4, PDB ID 8K5B). Atorvastatin, lanifibranor, Ezetimibe, and Niacin were used as standards.

***Results*:** The *in silico* analysis of both plants identified some compounds with binding energies ranging from -7.00 to -8.76 kcal/mol. Pyridine-3-carboxylic acid with binding energy -8.76 kcal/mol from *Cymbopogon citratus* possesses the greatest binding affinity, while the next was 7-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylhepta-2,4,6-trien-1-one (piperettine) with binding energy -8.57 kcal/mol from *Piper guineense*. (1S,2S,4aR,8aR)-2-(1,3-benzodioxol-5-yl)-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]-piperidin-1-ylmethanone) with binding affinity of 7.51 kcal/mol NCP1L1 (7WGN) is a promising ligand for drug.

***Conclusion*:** The findings suggest that both plants contain compounds with hypolipidemic activity, which justifies their traditional use in the treatment of hyperlipidemia. However, lead optimization and experimental validation will be required to confirm the outcome of this study.
***Keywords*:** *Cymbopogon citratus,* Hyperlipidemia, Phytoconstituents, *Piper guineense*, Protein targets.

1. INTRODUCTION

Hyperlipidemia is characterized by very high concentrations of lipids, which consist of cholesterol, lipoproteins, and triglycerides in the blood**.** It is one of the major predisposing factors of atherosclerotic cardiovascular disease (ASCVD), which includes high blood pressure, stroke, and heart attack, which are major causes of morbidity and mortality among the global population [1,2]. Since there has been an increase in global reports on lipid-related diseases, the World Health Organization (WHO) has embarked on a worldwide campaign to eliminate industrially manufactured trans fats in foodstuffs due to their contribution to ASCVD [3]. However, reports revealed their presence in our food [4]. A recent report has shown that approximately 1 in 3 adults (24.1%) worldwide have hypercholesterolemia that contributes to a considerable proportion of coronary events and cerebrovascular accidents [5]. In Nigeria, hyperlipidemia and lipid disorders have been on the increase [6]. Hyperlipidemia can be managed through non-pharmacological and pharmacological methods. These interventions must be applied either in isolation or as supplements to drug therapy [7]. The pharmacologic management of hyperlipidemia focuses on lowering low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and total cholesterol, and increasing high-density lipoprotein cholesterol (HDL-C) to prevent atherosclerotic cardiovascular disease (ASCVD) [8]. The Statins (3-Hydroxy-3-methylglutaryl-coenzyme A Reductase (HMG-CoA Reductase) Inhibitors), fibrates (Peroxisome Proliferator-Activated Receptor Gamma (PPAR) inhibitors), Niacin (Hydroxycarboxylic Acid

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Receptor 2 (HCAR2) inhibitor), ezetimibe (Niemann-Pick C1-Like 1 (NPC1L1) inhibitors), alirocumab (Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors) and omega-3 fatty acids are the major classes of drugs used in pharmacological management of hyperlipidemia [9,10]. Herbal and traditional medicines are still popular all over the world to prevent and treat metabolic diseases such as hyperlipidemia. *Cymbopogon citratus* (lemon grass) and *Piper guineense* (West African black pepper/uziza) are traditionally used in various tropical regions to manage hyperlipidemia (high cholesterol) and associated cardiovascular risks [11-14]. However, there is a paucity of information in human studies on dosage and safety profile [15-17]. Computer-Aided Drug Design (CADD) uses structural and chemical data to predict how drug candidate interacts with biological targets, estimate their binding affinities, and optimize their pharmacological properties before laboratory testing. CADD helps streamline the drug development process by reducing time, cost, and experimental workload while increasing the likelihood of success [18-19]. Therefore, computational predictions must be complemented with experimental validation to ensure reliability [20]. The adverse effects and cost-effectiveness of synthetic lipid-lowering drugs, as well as limited information on the dosage and safety of the use of herbs for the treatment of hyperlipidemia in humans, remain a major challenge. Consequently, this study aimed to evaluate the hypolipidemic potential, bioavailability, and toxicity profile of phytoconstituents in *Cymbopogon citratus* and *Piper guineense* using a computational approach.

2. MATERIALS AND METHODS

2.1 Materials

2.1.1 *Chemicals and Reagents*

Computer databases and web resources were used in the study. These include: Maestro software, PubChem (https://pubchem.ncbi.nlm.nih.gov/) information on *Cymbopogon citratus and Piper guineense*, Protein Data Bank (PDB) (https://www.rcsb.org/), SwissADME (http://www.swissadme.ch/), and the Protox-11 web server toxicity studies.

2.1.2 *Equipment and Other Materials*

A Computer System (Windows 10 Pro; Core i5, 2.40GHz; 16GB; 64-bit with an external pointing device).

2.2 Methods

2.2.1 *Ligand Selection and Preparation*

Phytoconstituents were selected from two Nigerian medicinal plants traditionally used to treat hyperlipidemia: *Cymbopogon citratus* and *Piper guineense* [21-24]. The structure data file (SDF) format for each phytochemical constituent was obtained from the PubChem database, and the standard ligands' (Atorvastatin, lanifibranor, Ezetimibe, and Niacin) SDF format was retrieved from PubChem as well. Ligand preparation was performed using the Ligprep panel in Maestro 12.8, employing the OPLS4 force field at pH 7.0 ± 2.0.

2.2.2 *Preparation of protein*

The target protein, 3-Hydroxy-3-methylglutaryl-coenzyme A Reductase (HMG-CoA Reductase, PDB ID 1HWK), was downloaded from the Protein Data Bank (PDB) (https://rcsb.org) and uploaded to the Maestro 12.8 workspace. Protein preparation involved using the Protein Preparation Wizard in the Schrödinger suite. In preprocessing, bond orders were assigned, waters within 5.0 Å of hetero groups were removed, pH was set at 7.0 ± 2.0, hydrogen bonds were added, and ions were removed. The refinement step optimized the H-bond network using PROPKA and removed water molecules with fewer than 3 H-bonds to non-water molecules. Subsequent restrained minimization was conducted using the OPLS4 force field with a Root-Mean-Square Deviation (RMSD) of 0.30 Å. The procedure was repeated using the proteins Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ, PDB ID 6ENQ), Hydroxycarboxylic Acid Receptor 2 (HM7A4, PDB ID 8K5B), and Niemann-Pick C1-Like 1 (NCP1L1, PDB ID 7WGN), respectively.

2.2.3 *Receptor Grid Generation*

The receptor grid file was generated using the receptor grid generation panel, delineating the receptor's active sites for Glide Ligand. Ligand docking was done within the active sites of hydroxyl methyl glutaryl CoA (HMG-CoA), peroxisome proliferator activated receptor (PPAR) gamma, hydroxylcarboxylic acid (HM7A4), and Niemann-Pick C1-Like 1 (NCP1L1). A grid box was defined around the active-site residues of each receptor, with dimensions of X: 20.0 Å, Y: 20.0 Å, and Z: 20.0 Å. These dimensions were chosen to ensure comprehensive coverage of the receptor-binding sites for effective ligand docking.

2.2.4 *Molecular Docking*

The prepared ligands underwent docking with the binding site of the proteins using High

Throughput Virtual Screening (HTVS) with non-refined ligand sampling.

2.2.5 *Post-Docking Analysis*

After molecular docking, the binding affinities of the docked ligands were compared with those of standard hypolipidemic reference compounds: atorvastatin, lanifibranor, Ezetimibe, and Niacin. Ligands that demonstrated binding affinities comparable to or better than these reference compounds were selected as promising candidates for further evaluation. The pharmacokinetic and toxicity profiles of the selected ligands were evaluated using SwissADME and ProTox-II, respectively, to assess their drug-likeness and safety. Thereafter, they were evaluated for oral bioavailability based on Lipinski's Rule of Five (RO5), which predicts drug-likeness using the standard criteria [25]. Ligands that complied with RO5 criteria were considered to have favorable oral bioavailability and were prioritized for further analysis.

2.2.6 *Data analysis*

Docking scores, which are measures of binding affinity values expressed in kcal/mol, obtained from the interaction between compounds (phytochemicals and reference ligands) and protein targets were analyzed descriptively. Comparative analyses of docking scores for phytochemicals and reference ligands were carried out based on their binding energies and interaction profiles.

2.3 Statistical Analysis

Docking scores were analyzed descriptively using binding affinity values expressed in kcal/mol, while Comparative analyses between reference ligands and phytochemicals were based on binding energies and interaction profiles. Validation of docking scores was carried out by re-docking the native ligand or co-crystallized ligand against the protein target. The selected ligands were evaluated for bioavailability based the results of ADMET profiles by using the Lipinski's Rule of Five (RO5), while the baseline for toxicity values of the ligands obtained from the toxicity profiles with Probability < 0.5000 predicts safe, and Probability > 0.5000 > 0.7000 predicts high and not safe.

3. RESULTS

The docking scores were obtained using Maestro, and those compounds or phytoconstituents with docking scores comparable to or greater than those of the reference ligands were subjected to further study. Hence, the results for the Binding Affinity Profile of reference ligands and selected compounds from *Cymbopogon citratus* (DC), Poaceae and *Piper guineense* are presented in Tables 1, 2, and 3, respectively. Furthermore, the results of two-dimensional interactions between promising phytochemicals and target proteins are shown in Figure 1 and Figure 2 below. The ADMET profiles for selected compounds from *Cymbopogon citratus* and *Piper guineense* with binding affinity greater than -7.00 kcal/mol were presented in Tables 4 and 5, respectively. This is because ≤-7.00 kcal/mol is widely considered the baseline or threshold for a promising ligand. Also, the results for the toxicity profiles of the compounds from *Cymbopogon citratus* and *Piper guineense* that passed Lipinski's rules of five (RO5) were presented in Tables 6 and 7, respectively.

Table 1: Docking scores of standard reference hypolipidemic drug

S/N	PubChem Compound CID	Compound Name	1HWK (kcal/mol)	6ENQ (kcal/mol)	8K5B (kcal/mol)	(7WGN) (kcal/mol)
1	60823	(3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid (Atorvastatin)	-5.40	=	=	=
2	68677842	4-[1-(1,3-benzothiazol-6-ylsulfonyl)-5-chloroindol-2-yl]butanoic acid (Lanifibranor)	=	-6.98	=	=
3	21829311	2-deuteriopyridine-3-carboxylic acid (Niacin)	=	=	-8.76	=
4	150311	(3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4(4hydroxyphenyl)azetidin-2-one (Ezetimibe)	=	=	=	-7.16

Table 2: Docking scores for *Cymbopogon citratus*

S/N	COMPOUND CID	IUPAC NAME	1HWK (kcal/mol)	6ENQ (kcal/mol)	8K5B (kcal/mol)	7WGN (kcal/mol)
1	938	Pyridine-3-carboxylic acid	-6.59	=	-8.76	=
2	6037	(2S)-2-[[4-[(2-amino-4-oxo-1H-pteridin-6-yl)methylamino]benzoyl]amino]pentanedioic acid	-7.43	-6.98	=	=
3	1794427	(1S,3R,4R,5R)-3-[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy-1,4,5-trihydroxycyclohexane-1-carboxylic acid (Chlorogenic acid)	-7.58	=	=	-7.45
4	5280373	5,7-dihydroxy-3-(4-methoxyphenyl)chromen-4-one	=	=	=	-7.40
5	5281804	5-hydroxy-3-(4-hydroxyphenyl)-7-methoxychromen-4-one	=	=	=	-7.28
6	15901362	(1R,3S,4S,5S)-1,3,4-trihydroxy-5-[(E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoyl]oxycyclohexane-1-carboxylic acid	=	-7.38	=	=
7	91825557	2-(3,4-dihydroxyphenyl)-5-hydroxy-7-methoxy-6-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]-4a,8a-dihydrochromen-4-one	=	-7.40	=	=
8	101105499	(2S)-4-[(E)-2-[(2R)-2-carboxy-5-hydroxy-6-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoyl]oxymethyl]oxan-2-yl]oxy-2,3-dihydroindol-1-yl]ethenyl]-2,3-dihydropyridine-2,6-dicarboxylic acid	-7.22	=	=	=
9	165359504	4-[2-[2-carboxy-5-hydroxy-6-[3,4,5-trihydroxy-6-[3-(4-hydroxyphenyl)prop-2-enoyloxymethyl]oxan-2-yl]oxy-2,3-dihydroindol-1-yl]ethenyl]-2,3-dihydropyridine-2,6-dicarboxylic acid	-7.86	=	=	=

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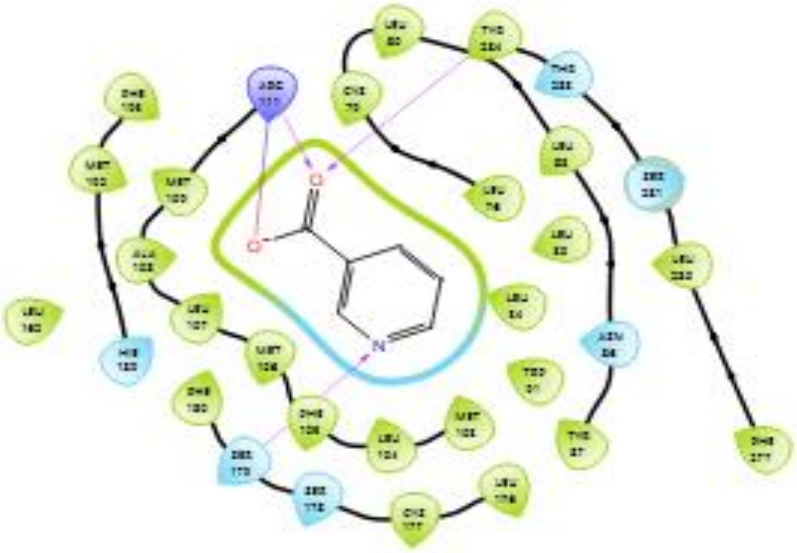
Table 3: Docking Scores of *Piper guineense*

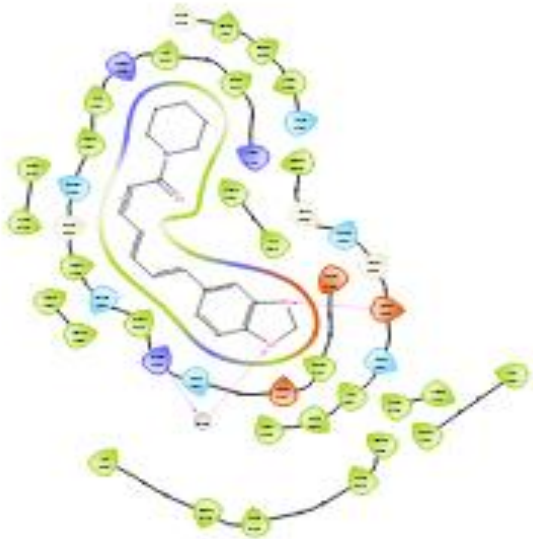
S/N	COMPOUND CID	IUPAC NAME	1HWK (kcal/mol)	6ENQ (kcal/mol)	8K5B (kcal/mol)	7WGN (kcal/mol)
1	4840	5-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylpenta-2,4-dien-1-one	=	-7.88	=	-7.72
2	54930	3-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylprop-2-en-1-one (Ilepcimide)	=	-7.15	=	-8.42
3	90785	2-(3,8-dimethyl-1,2,3,3a,4,5,6,7-octahydroazulen-5-yl)propan-2-ol	=	-7.08	=	=
4	117669	5-(1,3-benzodioxol-5-yl)-1-pyrrolidin-1-ylpenta-2,4-dien-1-on	=	-7.45	=	-8.02
5	155328	5-(6-methoxy-1,3-benzodioxol-5-yl)-1-piperidin-1-ylpenta-2,4-dien-1-one	=	=	=	-7.46
6	162986	5-(6-methoxy-1,3-benzodioxol-5-yl)-1-piperidin-1-ylpent-2-en-1-one	=	=	=	-7.77
7	276753	5-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylpent-2-en-1-one	=	=	=	-8.13
8	287685	3,4-bis(1,3-benzodioxol-5-ylmethyl)oxolan-2-ol	=	-7.00	=	-8.21
9	441005	(1S,8aR)-4,7-dimeth	=	-7.28	=	=
10	641115	(1S,8aR)-4,7-dimethyl-1-propan-2-yl-1,2,3,5,6,8a-hexahydronaphthalene	=	=	=	-8.42
11	1548913	(2Z,4E)-5-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylpenta-2,4-dien-1-one	=	=	=	-7.72
12	5281772	E)-3-(1,3-benzodioxol-5-yl)-N-(2-methylpropyl)prop-2-enamide	=	=	=	-7.32
13	5320618	(E)-5-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylpent-2-en-1-one	=	=	=	-7.50
14	5320621	(2E,4E)-5-(1,3-benzodioxol-5-yl)-N-(2-methylpropyl)penta-2,4-dienamide	=	=	=	-7.57
15	6429077	(1S,4S)-1,6-dimethyl-4-propan-2-yl-1,2,3,4-tetrahydronaphthalene	=	-7.26	=	=
16	6441090	(E)-5-(6-methoxy-1,3-benzodioxol-5-yl)-1-piperidin-1-ylpent-2-en-1-one	=	=	=	-7.77
17	11783540	[(1S,2S,4aR,8aR)-2-(1,3-benzodioxol-5-yl)-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]-piperidin-1-ylmethanone	=	=	=	-7.51
18	25021463	1-(2,4,5-trimethoxyphenyl)propane-1,2-diol	=	-7.00	=	=
			=	-7.52	=	-8.57
19	91274708	7-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylhepta-2,4,6-trien-1-one				

A




Charged (negative)
Charged (positive)
Glycine
Hydrophobic
Metal
Polar
Unspecified residue
Water
Hydration site
Hydration site (displaced)
Distance
H-bond
Halogen bond
Metal coordination
Pi-Pi stacking
Pi-cation
Salt bridge
Solvent exposure

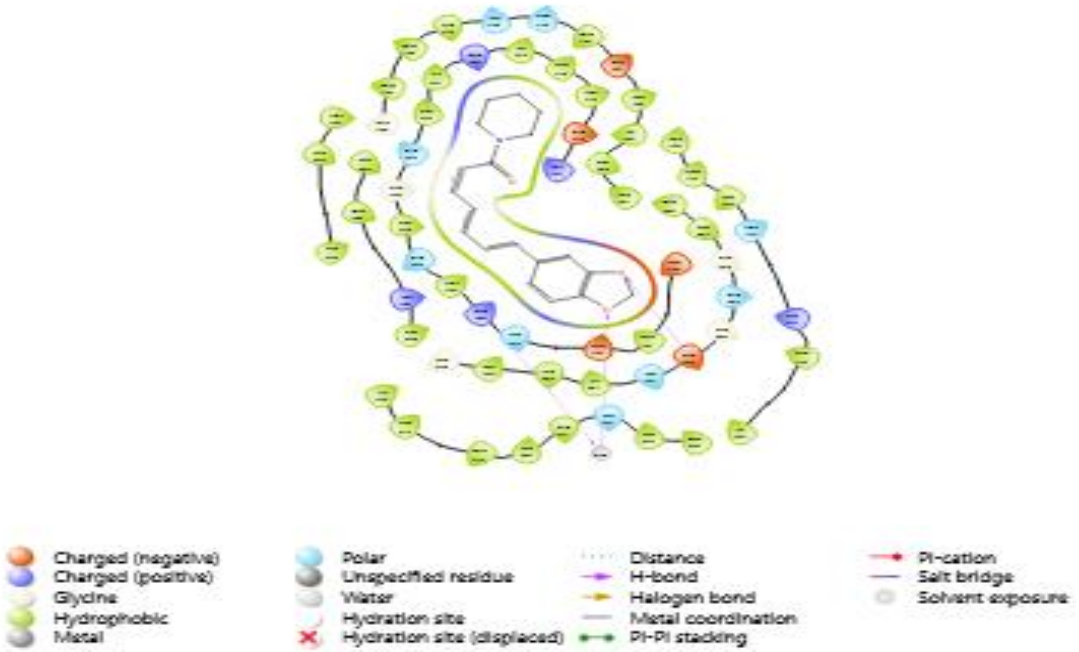
B




Charged (negative)
Charged (positive)
Glycine
Hydrophobic
Metal
Polar
Unspecified residue
Water
Hydration site
Hydration site (displaced)
Distance
H-bond
Halogen bond
Metal coordination
Pi-Pi stacking
Pi-cation
Salt bridge
Solvent exposure

Figure 1: 2D interactions of compounds with protein targets; **A**: 938 from *Cymbopogon citratus* with 8K5B, **B:** 91274708 *Piper guineense* with 7WG

A



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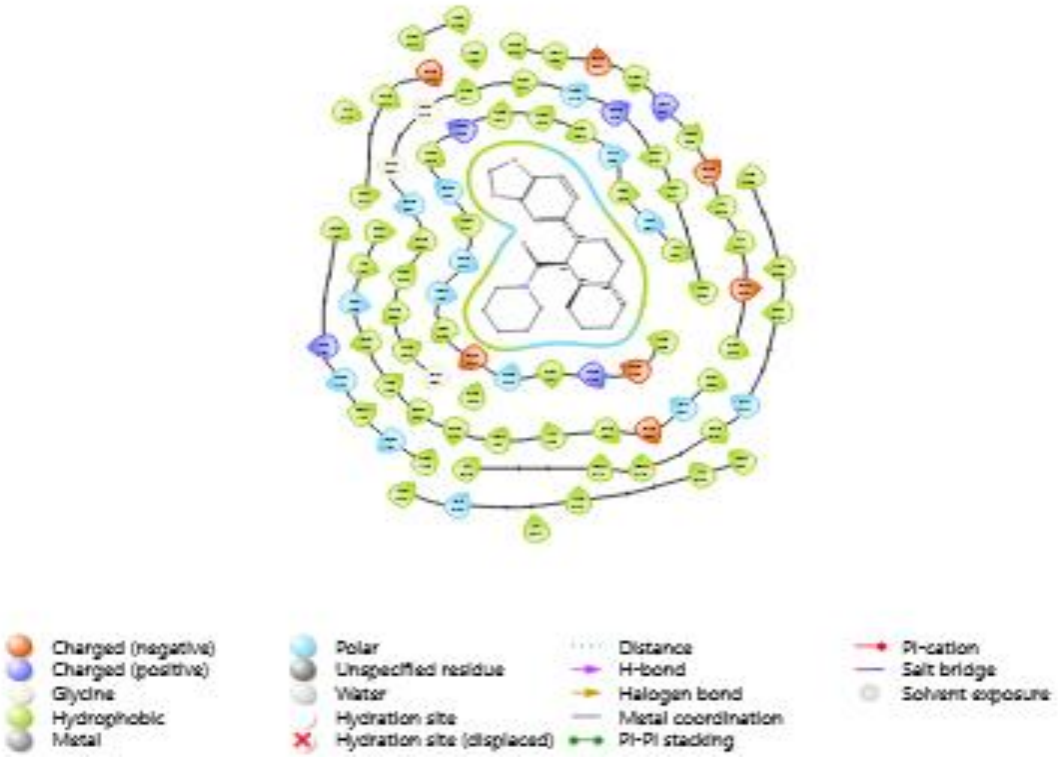

Figure 2: 2D interactions of compounds with protein targets; **A:** 91274708 *Piper guineense* with 6ENQ, **B:** 11783540 *Piper guineense* with 7WGN

Table 4: ADME profile of ligands from *Cymbopogon citratus*

S/N	Compound CID	Molecular weight	No of H-bond acceptors	No of H-bond donors	Consensus Log P	Lipinski	Bioavailability Score
1	938	102.09	3	2	-0.67	0	0.56
2	6037	441.4	9	6	-0.42	2	0.11
3	1794427	354.31	9	6	-0.39	1	0.11
4	5280373	284.26	5	2	2.44	0	0.55
5	5281804	284.26	5	2	2.43	0	0.55
6	15901362	368.34	9	5	-0.08	0	0.11
7	91825557	464.42	11	7	-0.95	2	0.11
8	101105499	726.64	17	8	-0.21	3	0.11
9	165359504	696.61	16	8	-0.17	3	0.11

Table 5: ADME profile of ligands from *Piper guineense*

S/N	Compound CID	Molecular weight	No of H-bond acceptors	No of H-bond donors	Consensus Log P	Lipinski	Bioavailability Score
1	4840	285.34	3	0	3.03	0	0.55
2	54930	259.3	3	0	2.52	0	0.55
3	90785	222.37	1	1	3.41	0	0.55
4	117669	271.31	3	0	2.75	0	0.55
5	155328	315.36	4	0	2.96	0	0.55

6	162986	317.38	4	0	3.00	0	0.55
7	276753	287.35	3	0	3.10	0	0.55
8	287685	356.37	6	1	2.90	0	0.55
9	441005	204.35	0	0	4.14	1	0.55
10	64115	208.22	3	0	0.35	0	0.55
11	1548913	285.34	3	0	0.35	0	0.55
12	5281772	247.29	3	1	2.65	0	0.55
13	5320618	287.35	3	0	3.10	0	0.55
14	5320621	273.33	3	1	3.17	0	0.55
15	6429077	202.34	0	0	4.57	1	0.55
16	6441090	317.38	4	0	3.00	0	0.55
17	11783540	367.48	3	0	4.09	0	0.55
18	25021463	356.37	6	1	3.00	0	0.55
19	91274708	311.37	3	0	3.55	0	0.55

Table 6**:** Toxicity profile of ligands from *Cymbopogon citratus*

S/N	Compound CID	Carcinogenicity	Genotoxicity	Hematotoxicity	Nephrotoxicity	Neurotoxicity	Ototoxicity	Respiratory
1	938	0.8405	0.7860	0.3920	0.6215	0.4133	0.1631	0.7034
2	1794427	0.2249	0.2433	0.0282	0.4406	0.0093	0.9216	0.1086
3	5280373	0.7460	0.9347	0.1401	0.2461	0.3040	0.1925	0.8436
4	5281804	0.7125	0.8561	0.1654	0.2358	0.3816	0.2239	0.7223
5	15901362	0.4211	0.5026	0.2574	0.8717	0.0339	0.5882	0.2630

Table 7: Toxicity profile of ligands from *Piper guineense*

S/N	Compound CID	Carcinogenicity	Genotoxicity	Hematotoxicity	Nephrotoxicity	Neurotoxicity	Ototoxicity	Respiratory
1	4840	0.6930	0.2430	0.2545	0.5243	0.7278	0.3702	0.6700
2	54930	0.6137	0.6170	0.3656	0.4940	0.7549	0.2496	0.5580
3	90785	0.7187	0.0067	0.4712	0.2794	0.4632	0.7040	0.6400
4	117669	0.7416	0.4872	0.2622	0.5371	0.7536	0.3642	0.6520
5	155328	0.7506	0.3400	0.3893	0.5750	0.7443	0.3252	0.7204
6	162986	0.5657	0.2342	0.4244	0.5281	0.6778	0.3607	0.7349
7	276753	0.4822	0.2388	0.4148	0.5661	0.6548	0.3727	0.7014
8	287685	0.5352	0.3035	0.3530	0.5942	0.7194	0.9333	0.5844
9	441005	0.6685	0.0644	0.6165	0.3485	0.5972	0.4594	0.6774
10	64115	0.7028	0.9846	0.5699	0.4627	0.8981	0.4008	0.7372
11	1548913	0.7346	0.7025	0.2527	0.4701	0.6452	0.2906	0.6301
12	5281772	0.6335	0.8062	0.2865	0.3139	0.6239	0.1867	0.2995
13	5320618	0.4183	0.7010	0.5029	0.6479	0.6781	0.4337	0.7424
14	5320621	0.6971	0.6886	0.2883	0.4277	0.6526	0.3043	0.5369
15	6429077	0.8177	0.0906	0.3275	0.3892	0.6551	0.3113	0.8825
16	6441090	0.4987	0.6074	0.4494	0.5780	0.7374	0.3669	0.7742
17	11783540	0.4053	0.0762	0.3747	0.4372	0.5823	0.3355	0.6048
18	25021463	0.8356	0.9955	0.6922	0.9516	0.9451	0.7272	0.6008
19	91274708	0.7745	0.2464	0.2739	0.5234	0.6861	0.3749	0.8209

4. DISCUSSION

The phytoconstituents of *Cymbopogon citratus* and *Piper guineense* were evaluated for their potential in managing and treating hyperlipidemia by docking them against 3-Hydroxy-3- -coenzyme A Reductase (HMG-CoA Reductase, PDB ID 1HWK), Peroxisome Proliferator methylglutaryl -Activated Receptor Gamma (PPAR-γ, PDB ID 6ENQ), Niemann-Pick C1-Like 1 (NCP1L1, PDB ID 7WGN) and Hydroxycarboxylic Acid Receptor 2 (HM7A4, PDB ID 8K5B), while atorvastatin, lanifibranor, ezetimibe and Niacin were used as reference standards respectively. These reference compounds are well-established hypolipidemic agents. The docking scores of the reference hypolipidemic agents served as benchmark values for evaluating the binding affinity of plant-derived ligands to the targeted receptors. The docking scores for the reference standard ranged from -5.40 kcal/mol to -8.76 kcal/mol, and more negative values indicate stronger interactions (Table 1). A total of 152 natural products of *Cymbopogon citratus* were downloaded from PubChem for docking studies. The docking scores for those compounds were analyzed for interactions with HMG-CoA (1HWK), PPAR-γ (6ENQ), HM7A4 (8K5B), and NCP1L1 (7WGN). The docking scores obtained indicated varying binding affinities of the phytoconstituents in *Cymbopogon citratus* to the selected protein targets, while the reference ligands served as a standard for comparison and further evaluation of potential new drug molecules. The compounds with binding affinity greater than -7.00 kcal/mol were selected for ADMET profiling and, thereafter, for toxicity profiling to determine drug likeness. The *in silico* analysis identified 9 compounds with binding energies ranging from -7.22 kcal/mol to -8.76 kcal/mol for *Cymbopogon citratus*. The results revealed that among the screened compounds, pyridine-3-carboxylic acid had the highest docking score of -8.76 kcal/mol in interaction with HM7A4 (8K5B), which was the same as that of one of the reference standards, Niacin (2-deuteriopyridine-3-carboxylic acid). Also, Pyridine-3-carboxylic acid (-6.59 kcal/mol HMG-CoA (1HWK), -8.76 kcal/mol HM7A4 (8K5B)) and (1S,3R,4R,5R)-3-[(E)-3-(3,4-dihydroxyphenyl)prop-2-enoyl]oxy-1,4,5-trihydroxycyclohexane-1-carboxylic acid (Chlorogenic acid) (-7.58 kcal/mol HMG-CoA (1HWK), -7.45 kcal/mol NCP1L1 (7WGN)) interacted with two of the protein targets in the lipid metabolism path way (Table 2).

A total of 141 compounds obtained from natural products of *Piper guineense* were retrieved from PubChem for docking studies. The docking scores for the compounds were based on the intensity of their binding with the selected protein targets. The in silico analysis identified 19 compounds with binding energies ranging from -7.00 to -8.46 Kcal/mol for *Piper guineense*. Among the compounds, 7-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylhepta-2,4,6-trien-1-one (piperetine) possesses the greatest binding energy of -8.57 kcal/mol on interaction with NCP1L1 (7WGN). This was followed by 3-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylprop-2-en-1-one and (1S,8aR)-4,7-dimethyl-1-propan-2-yl-1,2,3,5,6,8a-hexahydronaphthalene both with docking score of -8.42 kcal/mol NCP1L1 (7WGN)). In addition, five of the compounds displayed high docking scores ranging from -7.0 kcal/mol to 8.57 kcal/mol across two protein targets, PPAR-γ (6ENQ) and NCP1L1 (7WGN). These include three piperine derivatives (Table 3).

The results of molecular docking revealed that the interactions between Hyperlipidemia-related protein targets and phytoconstituents from *Cymbopogon citratus* and *Piper guineense* demonstrated strong binding affinities. In some cases, compounds interacted with two protein targets. The ability of CID 938 (Pyridine-3-carboxylic acid) (polar Niacin) to achieve high-affinity binding to HM7A4 (8K5B) (-8.76 kcal/mol) and HMG-CoA (1HWK) (-6.59 kcal/mol) suggests the receptor pocket is flexible with two distinct binding sites. Niacin binds competitively, using its pyridine nitrogen and carboxylic acid to interact with key polar parts in the known orthosteric pocket, stabilizing the active GPCR form (Figure 1A). The docking score performance was followed closely by CID 91274708 (7-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylhepta-2,4,6-trien-1-one (piperettine)) at -8.57 kcal/mol (NCP1L1 (7WGN). The exceptional affinity of CID 91274708 (piperettine) (-8.57 kcal/mol) towards NCP1L1 (7WGN) arises from optimal structural complementarity within the large, mostly hydrophobic LBD. The long alkyl chain and the aromatic benzodioxole ring structure of this amide derivative enhance van der Waals interactions with the lipophilic residues. This extensive hydrophobic contact provides a strong thermodynamic push for stabilization. At the same time, the amide oxygen atom is expected to form critical hydrogen bonds with key regulatory residues, which are vital for stabilizing the active conformation and allowing coactivator recruitment. The highly potent binding indicates that the chemical structure naturally has the necessary lipophilic dimensions and anchoring polar groups needed for effective NCP1L1 agonism (Figure 1B). In addition, CID 91274708 (piperettine) demonstrated good interaction with a docking score of -7.52 kcal/mol with PPAR-γ (6ENQ) (Figure 2A). Also, both CID 54930 3-(1,3-benzodioxol-5-yl)-1-piperidin-1-ylprop-2-en-1-one (Ilepcimide) and CID 641115 (1S,8aR)-4,7-dimethyl-1-propan-2-yl-1,2,3,5,6,8a-hexahydronaphthalene) had a docking score 8.42 kcal/mol on interaction with NCP1L1 (7WGN). SwissADME was employed to evaluate the pharmacokinetic properties of the phytoconstituents. It also assesses drug-likeness and medicinal chemistry friendliness using parameters such as molecular weight, lipophilicity, solubility, and bioavailability [26]. The evaluation is vital for identifying drug candidates with optimal bioavailability. The selected ligands were evaluated for bioavailability based on Lipinski's Rule of Five (RO5), which predicts drug-likeness using the following criteria: Molecular weight ≤ 500; LogP (lipophilicity) ≤ 5; Hydrogen bond donors ≤; Hydrogen bond

acceptors ≤ 10. Ligands that complied with RO5 criteria were considered to have favorable oral bioavailability and were prioritized for further analysis. These consist of compounds that did not break any of the rules [25]. The ADMET profile of ligands from *Cymbopogon citratus* showed that four out of the nine compounds selected after molecular docking did not pass RO5. In addition, all nineteen selected compounds from *Piper guineense* passed the RO5 (Table 4 and Table 5**)**. Compound CID 165359504 failed RO5 despite its high docking scores and interaction with multiple protein targets. The results from the toxicity profile of ligands that pass the Lipinski rule of five (RO5) are important for molecular drug design. The toxicity evaluated comprises carcinogenicity, genotoxicity, hematotoxicity, nephrotoxicity, neurotoxicity, ototoxicity, and respiratory toxicity. The results determine the druglikeness of the compounds. When the value is less than 0.5000, it predicts that it is safe. But when it is between 0.5000 and 0.7000 or more, it predicts it is not safe. Five compounds from *Cymbopogon citratus* were investigated for their toxicity; however, three of the compounds, CID 938, CID 5280373, and CID 5281804, had high carcinogenicity, genotoxicity, and respiratory toxicity values in the range of 0.9347 to 0.7034, while the fourth compound, CID 15901362, was considered nephrotoxic with a value of 0.8717 (Table 6). On the other hand, nineteen compounds from *Piper guineense* investigated exhibited varying levels of toxicity across the different toxicity parameters (Table 7). CID 641115, with a binding energy affinity of -8.42 kcal/mol, had a genotoxicity value of 0.9846, which made it unfit to be considered for further investigation. In addition, CID 91274708 had carcinogenicity, neurotoxicity, and respiratory toxicity values of 0.7745, 0.6861, and 0.8209, respectively. CID 938 (Pyridine-3-3-carboxylic acid) with binding energy affinity of -8.76 kcal/mol from *Cymbopogon citratus* possesses the greatest binding affinity; followed by CID 91274708, -8.76 kcal/mol; thereafter, CID 54930 and CID 641115 both with binding energy affinity of -8.42 kcal/mol all from *Piper guineense.* However, CID 938, CID 91274708, and CID 54930 are promising drug candidates because they interact with two of the protein targets in the lipid metabolism pathway. The identification of these compounds, alongside others in this study, as significantly stronger binders than Atorvastatin (CID 60823, -5.40 kcal/mol) suggests a strong theoretical capacity to inhibit endogenous cholesterol synthesis. CID 938 (polar Niacin) itself serves as a crucial reference. The structural and ADMET data from its unique mechanism (polar agonism at HM7A4) are essential for validating other lead compounds and guiding its structural improvements. The reference standard Niacin is the 2- deuterated form of CID 938. The structural modification must have significantly reduced its toxicity. Hence, it is used in the therapeutic management of hyperlipidemia. CID 91274708 in *Piper guineense* is one of the top candidates due to its unmatched potency against NCP1L1 (7WGN) -8.57 kcal/mol and PPAR-γ (6ENQ) (-7.52 kcal/mol). However, the high values of its carcinogenicity, nephrotoxicity, neurotoxicity, and respiratory toxicity, ranging from 0.8209 to 0.5234, indicate that structural optimization may be necessary for it to be orally relevant as a drug. It is very important to note that initial toxicological screening plays a crucial role in managing risks in chronic drug development [27]. It may require de-prioritizing some compounds despite their strong binding affinity, especially those with high genotoxicity and carcinogenicity [28]. CID 4840 and CID 54930, which bind to two protein targets in the lipid metabolic pathway, possess a good binding affinity in the range of -7.15 to -8.42 kcal/mol but have neurotoxicity values of 0.7278 and 0.7549, respectively (Tables 6 and 7). CID 11783540, a piperine analog with a binding affinity of -7.51 kcal/mol for NCP1L1 (7WGN), is a promising candidate for drug-likeness based on its ADMET profile and toxicity level among all the compounds investigated (Figure 2B). In addition, the study revealed that *Piper guineense* contains more hypolipidemic phytoconstituents and is less toxic than *Cymbopogon citratus.* Therefore, *Piper guineense* may be a preferred herb for treating hyperlipidemia compared with *Cymbopogon citratus.*

5. CONCLUSION

The study has predicted that *Cymbopogon citratus* and *Piper guineense* contain bioactive compounds with hypolipidemic activity, which could be explored for the discovery of a drug in the treatment of hyperlipidemia. The *in-silico* study indicated that *Piper guineense* contains more hypolipidemic phytoconstituents and is safer than *Cymbopogon citratus* as an herb. Experimental validation is required to translate these predictive findings into clinically viable therapeutic candidates.

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Conflict of Interest

The authors declare that they have no competing interests.

Contribution of the Authors

The study was conceived, designed, and supervised by Godfrey E. Aghayere. The Computational study and data collection were carried out by Uyi M. Ogbeide. Data analysis and interpretation were carried out by both Godfrey E. Aghayere and Uyi M. Ogbeide. Both authors contributed to the write-up, and approval was given by both.

Authors' Declaration
The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them. In addition, the authors declare that no AI-assisted tools were used.

Ethical Approval
Ethical approval was not required for this study because no human participants or experimental animals were involved.

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