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EXPLORING ANTIHYPERTENSIVE DRUG LEADS FROM *BLIGHIA SAPIDA* K. D. KOENIG VIA GC-MS AND IN SILICO APPROACHES

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Abstract: Globally, hypertension is a leading cause of cardiovascular diseases that account for around 17 million deaths. Despite more studies and management measures, the cause of hypertension is barely unknown, auxiliary antihypertensive medications have some drawbacks which include high prices, adverse effects, and resistivity. The little or no side effects posed by alternative medicines and patient compliance to medicinal plants raised interest in investigating *Blighia sapida* K. D. Koenig (Ackee) for its bioactive agents including proteins that could be responsible for its antihypertensive properties. Ethanol leave extract was analyzed using gas chromatography-mass spectrometry (GC-MS) analysis to detect the various bioactive compounds, two proteins that play prominent roles in hypertension were studied and retrieved for Molecular Docking using 3D crystal structures, wizard module of Schrödinger Maestro 12.8 employed to prepare the protein. The results of the docking computations were cleaned and analyzed using Excel spreadsheet software. Following receptor and ligand preparation, molecular docking computations were conducted using Glide's ligand docking plugin with extra precision docking to rigorously score ligand-protein interactions. Further graphical representations of the docking results were created using the R Studio package and GraphPad Prism V8.0. Visualization of the molecular interactions of the ligand-protein complexes was conducted. The GC-MS identified a total of 33 compounds in the ethanol extract: Benzenecarboximidothioic acid, N-phenyl-, 4-nitrophenyl ester, N-Serylserine and Palmitic Acid among others. During molecular docking, in-silico pharmacokinetics, and toxicological profiling, serylserine and pirenzepine were identified for their potential interactions with other important proteins related to hypertension including the calcium ion channel and the angiotensin II receptor (ARB). Serylserine and pirenzepine showed potential binding energy against the targeted proteins. This study could produce new antihypertensive medications that are less expensive, more widely available, and less likely to cause adverse effects, thereby meeting public health requirements, particularly in poor nations.

Keywords: *Blighia sapida*, hypertension, in-silico, molecular docking, pharmacokinetics, proteins, toxicology profiling.

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Introduction

Hypertension is a disease affecting individuals across all age groups; it is the most common cause of cardiovascular diseases all over the world and has been widely reported in Africa as a major cause of morbidity and mortality [ADELOYE & al. 2021]. According to the World Health Organization (WHO) 2016, about 17 million deaths have been recorded due to cardiovascular disease, of which 9.4 million of these deaths were caused by high blood pressure (HBP). In young adults, hypertension is mostly secondary but it is primary in adolescents and is therefore due to obesity [HASELER & SINHA, 2022]. Over the past few decades, the occurrence of hypertension has greatly increased in sub-Saharan Africa and there are expectations that the absolute value might be doubled in the year 2030 [ODILI & al. 2020].

In a recent cross-sectional survey conducted in Nigeria to assess the prevalence of hypertension among youth aged 18-35 years, studies revealed that the overall prevalence of hypertension in this age group was 15.2%, with higher rates observed among males compared to females [ABIODUN & al. 2021]. A wider coverage review ranging from the year 1968 to 2015 shows that the overall prevalence of hypertension ranges from 2.1% to 47.2% in adults and from 0.1 to 17.5% in children [SANI & al. 2024]. Hypertension and its complications constitute approximately 25% of emergency medical admissions in urban hospitals in Nigeria [ADELOYE & al. 2021].

Auxiliary drugs are extensively used in treating hypertension nationwide. Drugs such as amlodipine (Norvasc), felodipine (plendil), nifedipine (Procardia), nicardipine (Cardene), and more help to suppress the effect of high blood pressure. They control blood pressure by acting as angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and calcium channel blockers [NIAZI & al. 2023]. The adverse effects of these antihypertensive drugs are of great concern [KHAN & al. 2019] and the need therefore arises to consider herbal medicines in the management of high blood pressure due to their safety and fewer side effects.

Among the list of plants with medicinal potentials used in the management of hypertension in Nigeria is *Blighia sapida* K. D. Koenig (Ackee). Ackee is a native fruit of tropical West Africa that belongs to the family of Sapindaceae. This plant is known for its medicinal abilities in treating a wide range of ailments. All parts of this plant (bark, seed, root, fruit, capsule, leaves) can be used in treating: fever, malaria, internal haemorrhage, dysentery, burns, eyes inflammation, yellow fever, constipation, cutaneous infections, diarrhea, ulcers, yaws, intercostal pain, epilepsy and so on [RAMIREZ-SANTOS & al. 2023]. This study therefore focuses on the anti-hypertensive potential of *Blighia sapida* of leaf extract using gas chromatography-mass spectrometry and in-silico studies.

Material and methods

Plant collection and preparation

Leaves of *Blighia sapida* (Ackee) were collected from Olabisi Onabanjo University, Ago Iwoye, Ogun State and authenticated with herbarium deposit made at Forest Herbarium Institute of Nigeria with the voucher number 114066. Leaves were dried for three weeks in a cool, dry place with good ventilation. The plant material (200 g) was subjected to Soxhlet extraction using ethanol. The concentrated extracts were obtained by evaporating the solvent using a rotary evaporator.

The percentage yield of *Blighia sapida* was calculated as:

% Yield = weight of dried extract/weight of dried plant sample * 100

where: Weight of dried plant = 200 g, Weight of dried extract = 38.9 g, % Yield = 15.9/200 * 100, % Yield = 7.95%.

Gas Chromatography - Mass Spectrometry Analysis

The extracts were analyzed using an Agilent 8860 gas chromatograph equipped with a 5977B mass spectrometry detector (MSD) system, fitted with an Elite 5MS (5% diphenyl/95% dimethyl polysiloxane) fused capillary column (30 × 0.25µm ID × 0.25 µm df). For GCMS detection, an electron ionization system operated in electron impact mode with an ionization energy of 70 eV. Helium gas (99.999%) was used as a carrier gas at a constant flow rate of 1 ml/min, with an injection volume of 1µl (split ratio of 10:1). The injector temperature was maintained at 300 °C. The ion source temperature was 250 °C. The GC oven temperature was programmed from 110 °C (1 min), then ramped at 15 °C/min to 310 °C (2 min). Mass spectra were taken at 70 eV with a scanning interval of 0.5 s and fragments from 45 to 450 Da. The solvent delay was 0 to 3 min.

Identification and retrieval of proteins

Two proteins that play prominent roles in hypertension were studied and retrieved for Molecular Docking. These biomolecules were retrieved in their 3D crystal structures from PDB in PDB file format. The proteins are Angiotensin II Receptor with PDB ID 4YAY and L-type Calcium Ion Channel with PDB ID 8E59.

Preparation of proteins

The biomolecules underwent preparation using the protein preparation wizard module of Schrödinger Maestro 12.8. This process included preprocessing to assign bond orders and hydrogen bonds, reconstruct missing side chains and loops, and delete water molecules beyond 4Å from the het group [OLANREWAJU & al. 2024; MADHAVI SASTRY & al. 2013]. Subsequently, the hydrogen bond network was optimized, and heavy atoms were minimized. Binding sites were mapped, and grids were generated using the Glide plugin grid generation module in Maestro Schrödinger [OLANREWAJU & al. 2024; OLUGBOGI & al. 2023]. For proteins with unknown binding sites, computational mapping was performed using the Sitemap tool before grid generation [OLANREWAJU & al. 2024; HALGREN, 2009].

Retrieval and preparation of ligand

Thirty-three phytocompounds from Ackee were retrieved from the PubChem database in SDF format after being identified from the GCSM result. These compounds were prepared using LigPrep in the Schrödinger suite, utilizing the OPLS4 forcefield module for minimization.

Molecular docking

Following receptor and ligand preparation, molecular docking computations were conducted using Glide's ligand docking plugin with extra precision docking to rigorously score ligand-protein interactions.

Binding free energy calculations

The relative binding free energy (ΔG bind) of the ligand-protein complex was calculated using the Prime MMGBSA method (OLANREWAJU & al. 2024; BORKOTOKY & al. 2016). The formula used was: $\Delta G(bind) = \Delta G(solv) + \Delta E(MM) + \Delta G(SA)$

Where:

- ΔG solv. Represents the difference in GBSA solvation energy of the protein-ligand complex and the sum of the solvation energies for the free proteins and ligands.
- ΔE MM is the difference in the minimized energies between the protein-ligand complex and the sum of the energies for free proteins and ligands.
- ΔG SA is the difference in surface area energies of the complex and the sum of the surface area energies for the free proteins and ligands.

Prime MMGBSA computes the energy of optimized free receptors, free ligands, and ligand-protein complexes. Additionally, the ligand strain energy was calculated by immersing the ligands in a solution generated by the VSGB suite. This comprehensive approach allows for a detailed assessment of the energetics and stability of ligand-protein interactions.

Pharmacokinetic screening

The hit ligands underwent a virtual screening procedure based on Lipinski's "rule of five," Veber's rule, Ghose's rule filters, and toxicity parameters. Physicochemical properties, including drug-likeness and toxicity, were calculated using the Protox II web server, DataWarrior program version 4.6.1 [OLANREWAJU & al. 2024; SANDER & al. 2015], and AdmetSar web server. These calculations were performed by importing the ligands' mol.sdf and canonical smile format, allowing for a comprehensive assessment of their pharmacological and safety profiles.

Data snalyses and visualization

The results of the docking computations were cleaned and analyzed using Excel spreadsheet software. Further graphical representations of the docking results were created using the R Studio package and GraphPad Prism V8.0. Visualization of the molecular interactions of the ligand-protein complexes was conducted using Discovery Studio version 2021 and PyMOL visualizer.

Results and discussion

Computer-aided drug design (CADD) employs variety of computational techniques and algorithms to streamline drug discovery and development [NIAZI & al. 2023]. A crucial aspect of CADD is molecular docking, which forecasts the binding affinity and interactions between small molecule ligands and target proteins, offering valuable insights into their therapeutic potential [BAIG & al. 2018]. Through systematic computational analyses, lead compounds from *Blighia sapida* that could serve as promising candidates for further preclinical and clinical evaluation were identified, ultimately contributing to the advancement of personalized medicine strategies for hypertensive patients. For example, used CADD methods to assess the antihypertensive properties of peptides derived from *Acheta domesticus*. Similarly, CADD was employed as a supplemental technique by AKINTUNDE & al. (2022) to validate in vitro experiments that targeted proteins associated with hypertension.

The present study endeavors to harness computational methodologies, particularly molecular docking and in silico ADMET screening, to explore the therapeutic promise of phytochemicals derived from *Blighia sapida*. An essential part of the renin-angiotensin system (RAS), which controls blood pressure by fluid balance and vasoconstriction, is the Angiotensin II receptor, mainly type 1 (AT1). Blood pressure rises when angiotensin II activates this receptor. Conventional medications that target this receptor, such as losartan and other angiotensin receptor blockers (ARBs), function by opposing AT1, which reduces blood pressure and vasoconstriction [DINGEO & al. 2023].

The activity of calcium ion channels affects cardiac output and vascular resistance, which are crucial for controlling heart rate and vascular smooth muscle tone. Calcium channel blockers (CCBs), which include verapamil and nifedipine, work by blocking these channels. This results in vasodilation and a slowed heart rate which lowers blood pressure. These medications help treat hypertension because they directly alter the vascular smooth muscle's contractility, which affects systemic vascular resistance [HARRAZ & JENSEN, 2021]. By targeting these proteins, *Blighia sapida* compounds not only counteract the immediate processes

that contribute to high blood pressure but also provide insights into the larger regulatory networks that may be used to build more refined therapeutic approaches.

The docking computation results demonstrated promising therapeutic capabilities of the phytocompounds from *Blighia sapida*. Table 2 and table 3 present the docking scores and the binding free energy calculations, measured in kcal/mol. *Blighia sapida* phytocompounds demonstrated substantial inhibitory effects against the two key protein targets in hypertension.

The phytocompounds contained in *Blighia sapida* also showed minimal potential in reducing blood pressure and preventing vasoconstriction via inhibiting angiotensin II receptor. Among the phytocompounds, serylserine has the highest docking score (-8.932 kcal/mol) and the lowest binding free energy (-22.72 kcal/mol). This suggests it might have the strongest potential for binding to the AT1R. The remaining phytocompounds (palmitic acid, benzenecarboximidothioic acid, and D-allose) have lower docking scores and higher binding free energies than serylserine, suggesting weaker interactions with the AT1R.

The standard drug, losartan, has a docking score (-9.133 kcal/mol) that is slightly lower than serylserine, but its binding free energy (-66.53 kcal/mol) is significantly lower. This indicates that losartan has a much stronger overall binding affinity.

Biomedical researchers have shown a strong interest in inhibiting or blocking calcium ion channel subunits in the treatment of high blood pressure. Among the phytocompounds, pirenzepine has the highest docking score (-8.024 kcal/mol) and the lowest binding free energy (-23.38 kcal/mol), suggesting it might have the strongest potential for binding to the L-type calcium ion channel, while the remaining phytocompounds (benzenecarboximidothioic acid, 4-O-methylmannose, and phytol) have lower docking scores and higher binding free energies than pirenzepine, suggesting weaker interactions with the L-type calcium ion channel.

Medication absorption and metabolism are highly influenced by molecular weight (MW), with lower MW frequently resulting in more effective metabolism. This is critical in the treatment of hypertension, because effective medication distribution and avoidance of unnecessary tissue buildup are critical. Table 4 summarizes the key properties of the identified hit compounds from *Blighia sapida* and compares them to standard drugs using the SwissADME server.

Serylserine has a low molecular weight, good hydrogen bond donor/acceptor potential (indicated by Number of H-Bond Acceptors (HA) and Number of H-Bonds (HD)), and low Topological Polar Surface Area (TPSA). This suggests good water solubility and potentially good oral bioavailability also confirmed in Figure 12(a), Serylserine also has a low predicted P-glycoprotein (Pgp) substrate score and low reactive oxygen species (#ROS), suggesting potentially good absorption and lower risk of oxidative stress. However, it is not predicted to be blood–brain barrier (BBB) permeable. Palmitic Acid has a high iLogP value, indicating high-fat solubility and potentially lower oral bioavailability, it is predicted to be a Pgp substrate and may have lower absorption due to P-glycoprotein efflux. It also interacts with multiple CYP enzymes, potentially leading to drug interactions. Benzenecarboximidothioic acid has a high molecular weight, TPSA, and good predicted GI absorption, it has a low predicted Pgp substrate score and #ROS, but may have lower bioavailability due to its inability to cross the BBB. D-Allose similar to serylserine, has good water solubility and potentially good oral bioavailability, it has a low predicted Pgp substrate score and #ROS. The standard drug, amlodipine, has a lower docking score (-7.478 kcal/mol) but a significantly lower binding free energy (-8.932 kcal/mol). This indicates that amlodipine has a much stronger overall binding affinity.

The strategic application of ADMET profiling does not only speed up the drug development process but also increases the possibility of developing effective and safe

medicines tailored to manage and reduce high blood pressure, eventually improving patient outcomes in hypertension management.

Table 1. Gas chromatography-mass spectrometry results

S/N	RT (mins)	Proposed compound	Molecular formula	Molecular weight (/mol)	Area %	Quality
1.	3.230	beta-D-Glucopyranose, 1,6-anhydro-	$C_6H_{12}O_6$	180.16	2.22	9
2.	6.824	1,3,5-Triazine-2,4(1H,3H)-dione	$C_3H_3N_3O_2$	113.08	0.71	25
3.	10.469	1-Nonadecene	$C_{19}H_{38}$	266.5	0.58	94
4.	9.919	2(4H)-Benzofuranone, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-	$C_{11}H_{16}O_2$	180.24	0.41	96
5.	7.465	2-Methoxy-4-vinyl phenol	$C_9H_{10}O_{12}$	150.17	0.44	90
6.	12.031	3-Hexanol, 2,4-dimethyl-	$C_8H_{18}O$	130.229	7.61	38
7.	7.465	3-Methoxyacetophenone	$C_9H_{10}O_2$	150.17	0.44	80
8.	6.824	4-Fluoro-6-aminopyrimidine	$C_4H_4FN_3$	113.09	0.71	43
9.	10.154	4-Hydroxy-2-mercapto pteridine	$C_6H_4N_4OS$	180.19	0.64	43
10.	10.154	4-Methyl-2,5-dimethoxybenzaldehyde	$C_{10}H_{12}O_3$	180.2	0.64	47
11.	11.819	4-O-Methylmannose	$C_7H_{14}O_6$	194.18	39.77	53
12.	12.202	5,5,8a-Trimethyldecalin-1-one	$C_{13}H_{22}O$	194.31	1.81	43
13.	6.824	6H-Pyrido[2,3-b][1,4]benzodiazepine	$C_{19}H_{21}N_5O_2$	351.4	0.71	22
14.	10.469	9-Eicosene, (E)-	$C_{20}H_{40}$	280.5	0.58	94
15.	10.154	Benzenamine, N-(phenyl)(4-nitrophenylthio)methylene-	$C_{19}H_{14}N_2O_2S$	334.4	0.64	43
16.	4.747	Benzoic acid, methyl ester	$C_8H_80_2$	136.15	1.80	87
17.	19.555	Bis(2-ethylhexyl) phthalate	$C_{24}H_{38}O_4$	390.6	0.78	72
18.	9.484	D-Allose	$C_6H_{12}O_6$	180.16	1.34	90
19.	10.469	E-14-Hexadecenal	$C_{16}H_{30}O$	238.41	0.58	91
20.	3.230	Glycerin	$C_3H_8O_3$	92.09	2.22	9
21.	13.484	Hexadecanoic acid, methyl ester	$C_{17}H_{34}O_2$	270.5	1.92	91
22.	3.230	Hydroxyethyl butyl sulfide	$C_6H_{14}OS$	134.24	2.22	9
23.	12.946	Neophytadiene	$C_{20}H_{38}$	278.5	0.61	99
24.	17.083	n-Heptyl methylphosphonofluoridate	$C_8H_{18}FO_2P$	196.2	0.43	43
25.	13.805	n-Hexadecanoic acid	$C_6H_{32}O_2$	256.42	6.72	98
26.	11.819	N-Serylserine	$C_6H_{12}N_1O_5$	192.17	39.77	50
27.	15.361	Octadecanoic acid	$C_{18}H_{36}O_{20}$	284.5	1.00	99
28.	15.184	Oleic Acid	$C_{18}H_{34}O_2$	282.5	2.20	98
29.	19.229	Oxirane, [(dodecyl oxy)methyl]-	$C_{15}H_{30}O_2$	242.4	0.55	49
30.	7.465	Phenol, 2,3,5,6-tetramethyl-	$C_{10}H_{14}O$	150.22	0.44	64
31.	14.978	Phytol	$C_{20}H_{40}O$	296.5	3.41	91
32.	11.104	Thiophene, 2-ethyltetrahydro-	$C_6H_{12}S$	116.23	9.55	35
33.	11.104	Trimethylsilyl 14-acetoxy-3,6,9,12	$C_{15}H_{30}O_8Si$	366.48	9.55	43

Table 2. Type-1 angiotensin II receptor (human)

S/N	Plant Phytocompounds	Docking Scores (kcal/mol)	Binding free Energy (kcal/mol)
1.	Serylserine	-8.932	-22.72
2.	Palmitic Acid	-7.379	-46.31
3.	Benzenecarboximidothioic acid, N-phenyl-, 4-nitrophenyl ester	-7.322	-68.99
4.	D-Allose	-6.879	-26.54
5.	Losartan	-9.133	-66.53

Table 3. L-type Calcium ion Channel

S/N	Plant Phytocompounds	Doocking Scores (kcal/mol)	Binding free Energy (kcal/mol)
1.	Pirenzepine	-8.024	-23.38
2.	Benzenecarboximidothioic acid, N-phenyl-, 4-nitrophenyl ester	-6.921	-51.07
3.	4-O-Methylmannose	-6.633	-23.71
4.	Phytol	-6.272	-55.75
5.	Amlodipine	-7.478	-8.932

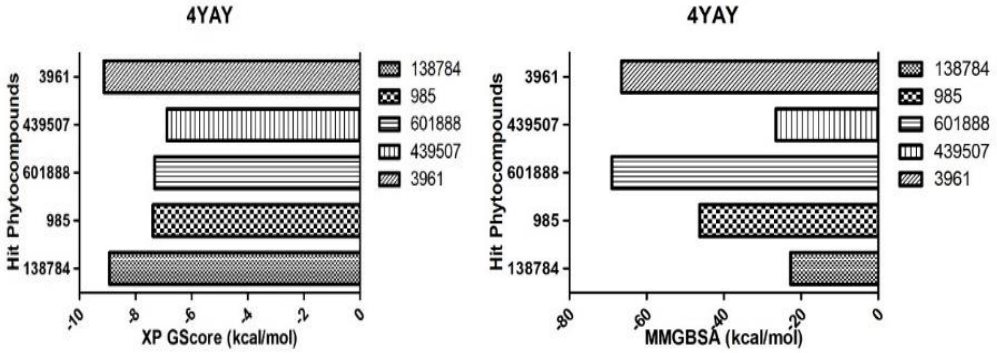

Figure 1. The differences in binding scores (MMGBSA and XP SCORE) of the hit compound from *Blighia sapida* alongside standard drug against Type-1 angiotensin II receptor (human).

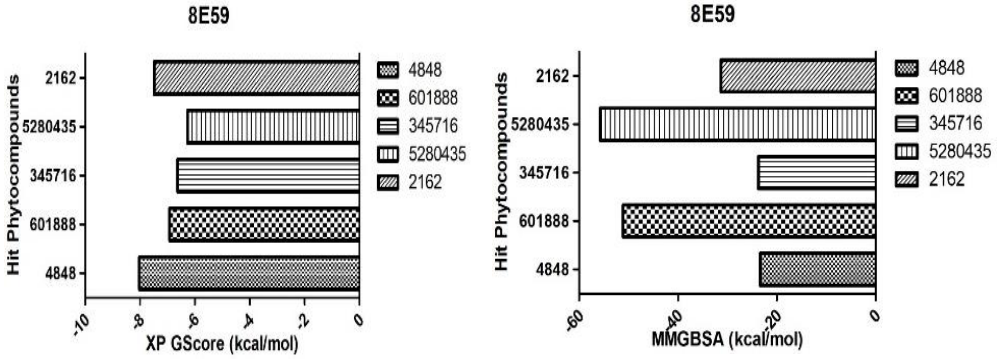

Figure 2. The differences in binding scores (MMGBSA and XP SCORE) of the hit compound from *Blighia sapida* alongside standard drug against L-type Calcium Ion Channel

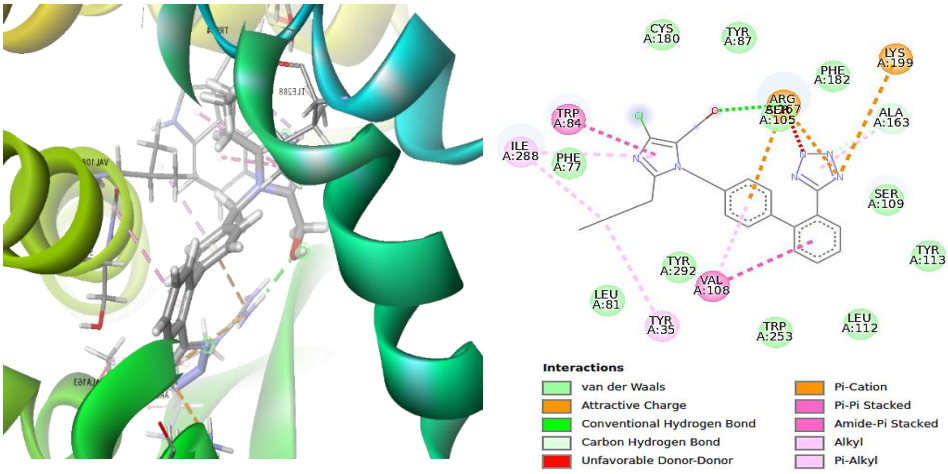

Figure 3. The 3D and 2D depictions illustrate the molecular interaction between the pharmacophoric moieties of Losartan and the key amino acid residues located at the binding site of Type-1 angiotensin II receptor (human)

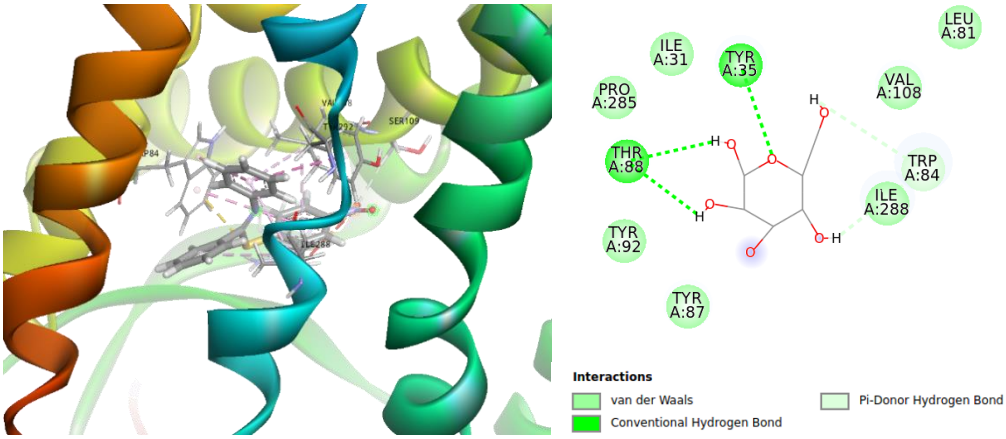

Figure 4. The 3D and 2D depictions illustrate the molecular interaction between the pharmacophoric moieties of D-Allose and the key amino acid residues located at the binding site of Type-1 angiotensin II receptor (human)

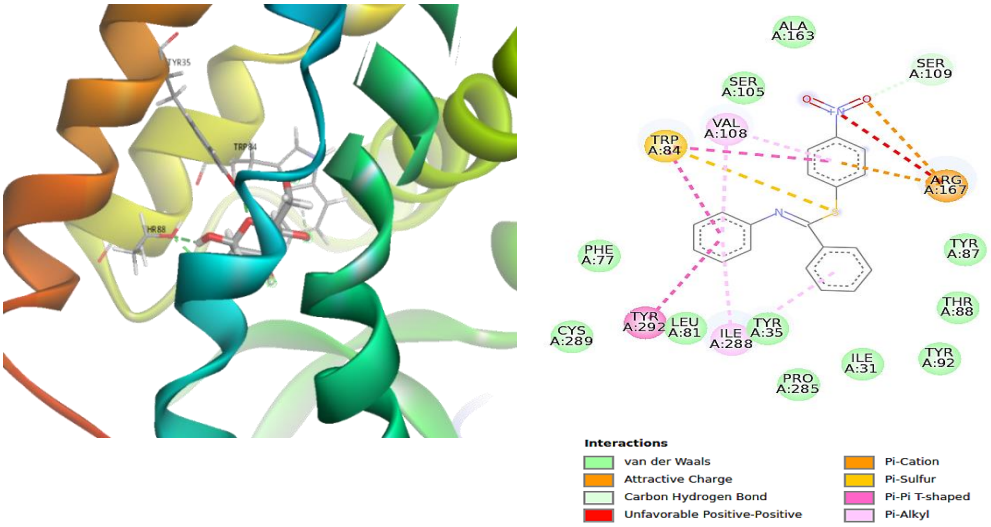

Figure 5. The 3D and 2D depictions illustrate the molecular interaction between the pharmacophoric moieties of Benzenecarboximidothioic acid, N-phenyl-, 4-nitrophenyl ester, and the key amino acid residues located at the binding site of Type-1 angiotensin II receptor (human)

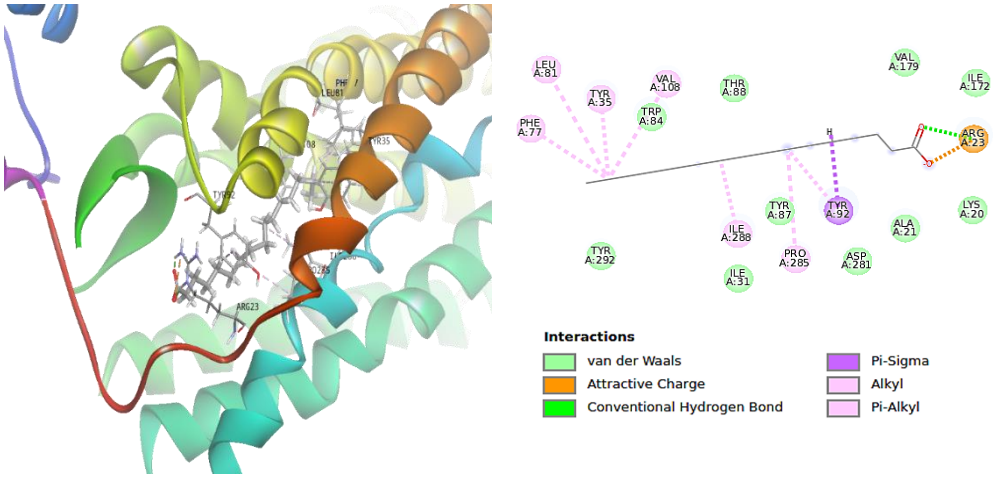

Figure 6. The 3D and 2D depictions illustrate the molecular interaction between the pharmacophoric moieties of palmitic acid and the key amino acid residues located at the binding site of Type-1 angiotensin II receptor (human)

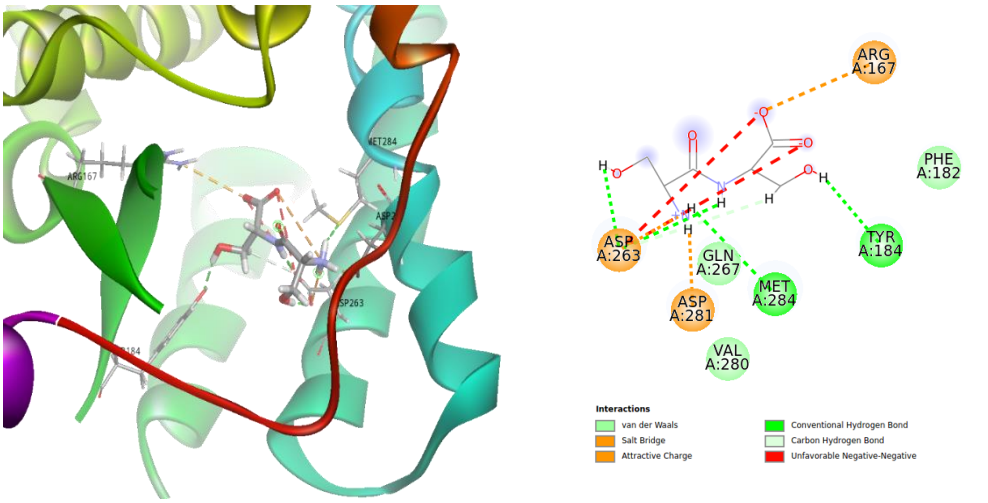

Figure 7. The 3D and 2D depictions illustrate the molecular interaction between the pharmacophoric moieties of Serylserine and the key amino acid residues located at the binding site of Type-1 angiotensin II receptor (human)

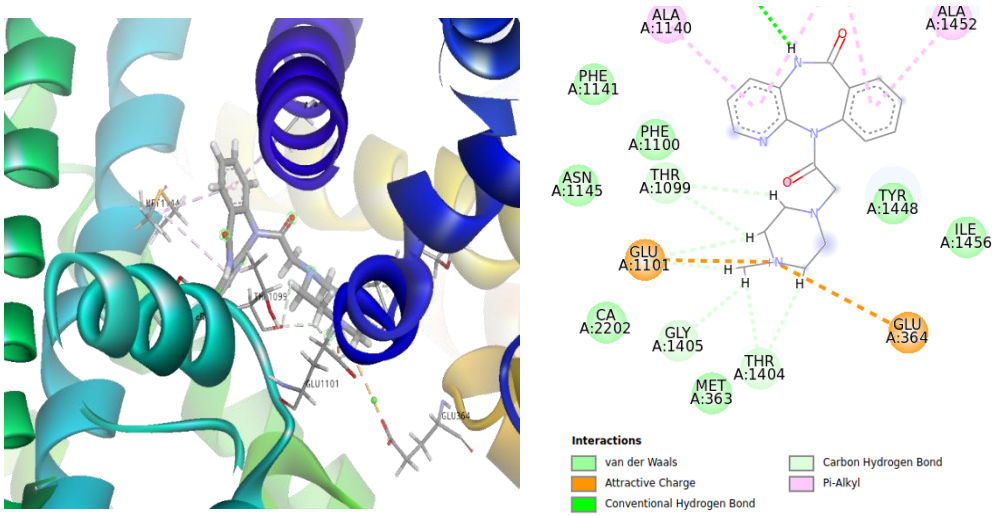

Figure 8. The 3D and 2D depictions illustrate the molecular interaction between the pharmacophoric moieties of Pirenzepine and the key amino acid residues located at the binding site of L-type Calcium Ion Channel

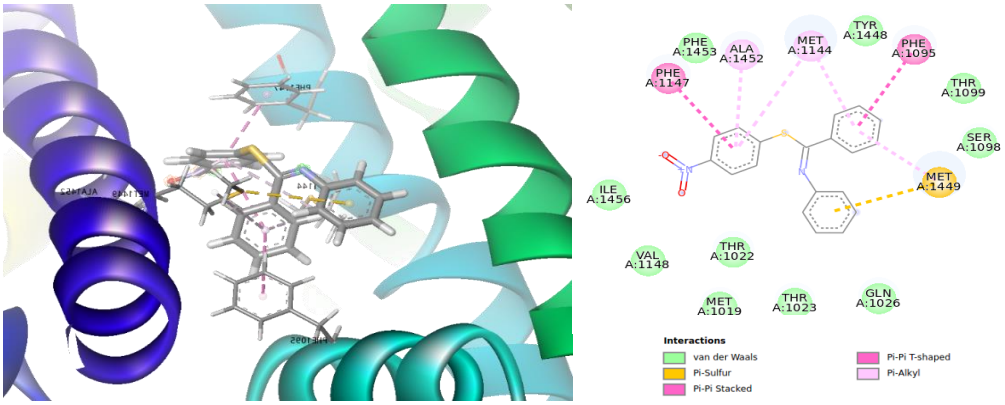

Figure 9. The 2D and 3D depictions illustrate the molecular interaction between the pharmacophoric moieties of Benzenecarboximidothioic acid, N-phenyl-, 4-nitrophenyl ester, and the key amino acid residues located at the binding site of L-type Calcium Ion Channel

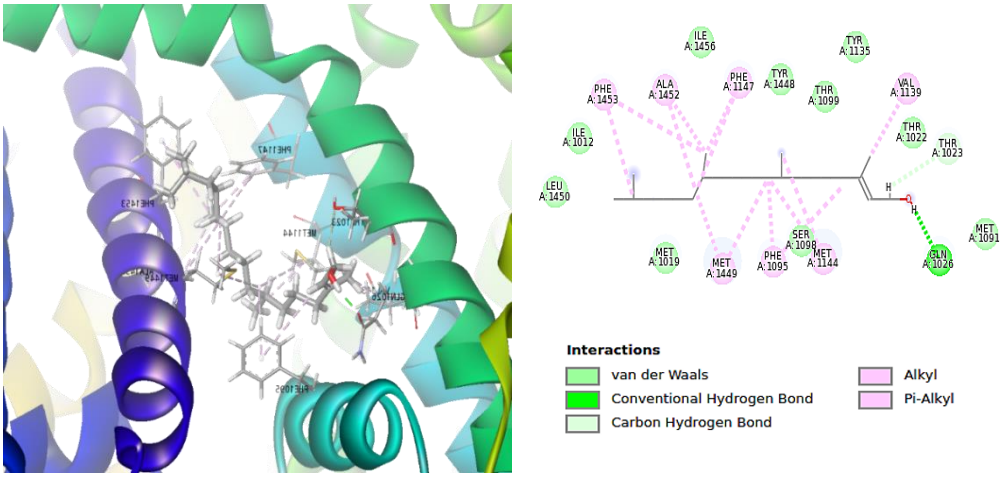

Figure 10. The 2D and 3D depictions illustrate the molecular interaction between the pharmacophoric moieties of Phytol and the key amino acid residues located at the binding site of L-type calcium ion channel

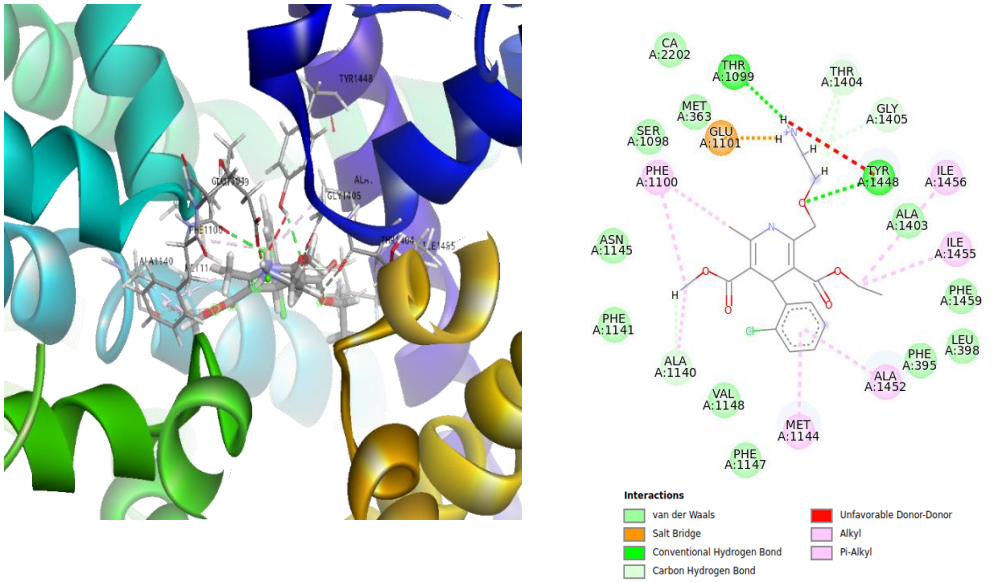

Figure 11. The 2D and 3D depictions illustrate the molecular interaction between the pharmacophoric moieties of Amlodipine and the key amino acid residues located at the binding site of L-type calcium ion channel

Table 4. Physiochemical, pharmacokinetics, and medicinal chemistry properties of the hit compounds and the standards (in bold letters) using the SwissADME server

PubChem CID	Compound Name	Mol/W	MR	iLogP	HA	HD	TPSA	GI absorption
138784	Serylserine	192.17	40.76	0.04	6	6	132.88	Low
985	Palmitic Acid	256.42	80.8	3.85	2	1	37.3	High
601888	Benzenecarboximidothioic acid, N-phenyl-, 4-nitrophenyl ester	334.39	100.2	2.84	3	0	83.48	High
439507	D-Allose	180.6	35.74	-0.7	6	5	110.38	Low
4848	Pirenzepine	351.4	108.71	2.37	5	1	74.23	High
345716	4-O-Methylmannose	194.18	40.47	0.52	6	4	99.38	Low
5280435	Phytol	296.53	98.94	4.85	1	1	20.23	Low

Table 4. (Cont'd)

PubChem CID	BBB Permeant	Pgp substrate	#ROS	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 Inhibitor	Bioavailability Score
138784	No	No	06	No	No	No	No	No	0.55
985	Yes	No	14	Yes	No	Yes	No	No	0.85
601888	No	No	05	Yes	Yes	Yes	No	No	0.55
439507	No	Yes	01	No	No	No	No	No	0.55
4848	No	Yes	03	No	No	No	No	No	0.55
345716	No	Yes	02	No	No	No	No	No	0.55
5280435	No	Yes	13	No	No	Yes	No	No	0.55

Keys: MW: Molecular weight; HA; Number of H-Bond Acceptors, HBD: Number of H-Bonds; TPSA: Topological Polar Surface Area; GI: Gastrointestinal, BBB: Blood–Brain Barrier; P-gp: P Glycoprotein; #RO5: Violations of Lipinski rule of five, MR: modified release, CYP1A2 inhibitors: a selective serotonin reuptake inhibitor used to treat obsessive-compulsive disorder, CYP3A4: is the primary cyp expressed postnatally, CYP2D6: mediates the metabolism of substrate psychotropic drugs, CYP2C9: the enzyme primarily responsible for the metabolism of warfarin's active S-enantiomer, CTP2C19: the principal enzyme involved in the hepatic metabolism of drugs.

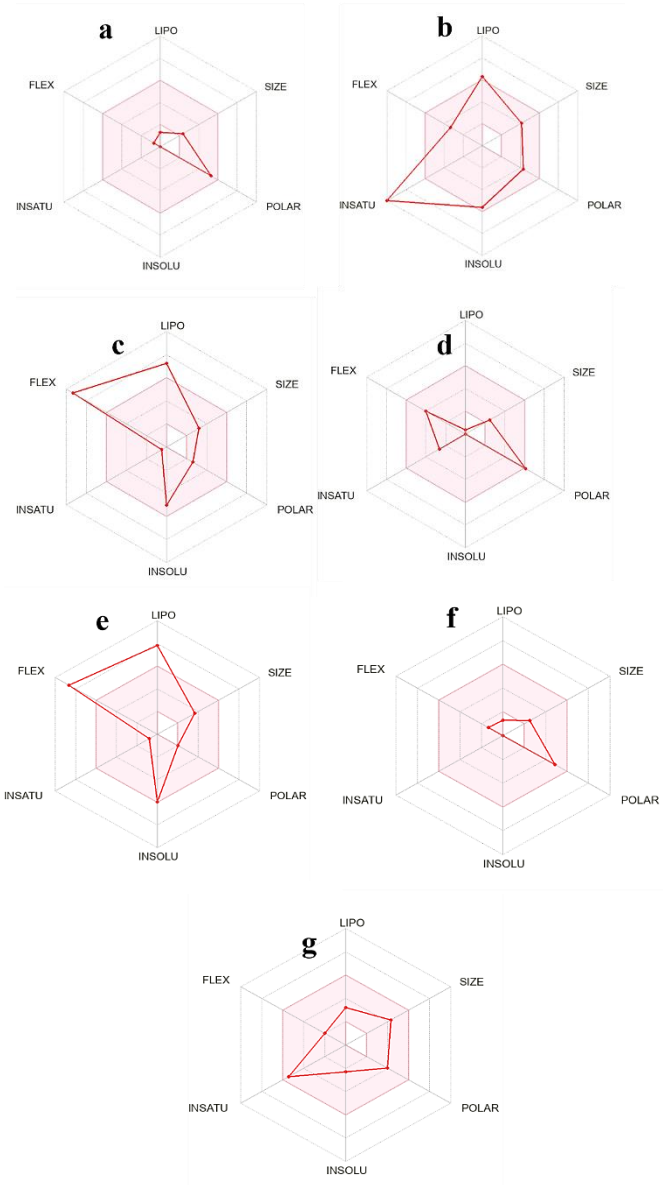

Figure 12. The bioavailability radar of the hit phytocompounds and standard drugs describing the physicochemical properties and drug-likeness of these compounds. The pink lines border within the acceptable range for each of the parameters measured by radar numbers and their corresponding compounds, where (a) represents the bioavailability radar for Serylserine (b) represents the bioavailability radar for Palmitic Acid (c) represents the bioavailability radar for Benzenecarboximidothioic acid, N-phenyl-, 4-nitrophenyl ester (d) represents the bioavailability radar for D-Allose (e) represents the bioavailability radar for Pirenzepine (f) represents the bioavailability radar for 4-O-Methylmannose (g) represents the bioavailability radar for Phytol

Table 5. The toxicity result of hit phytocompounds using Protox II server

Compounds	Hepatotoxicity	Neurotoxicity	Nephrotoxicity	Respiratory toxicity	Cardiotoxicity	Carcinogenicity
Serylserine	Inactive	Inactive	Active	Inactive	Active	Inactive
Palmitic Acid	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Benzenecarboximidothioic acid, N-phenyl-, 4-nitrophenyl ester	Active	Inactive	Inactive	Inactive	Active	Inactive
D-Allose	Inactive	Inactive	Inactive	Active	Active	Inactive
Pirenzepine	Active	Inactive	Inactive	Inactive	Active	Inactive
4-O-Methylmannose	Active	Inactive	Inactive	Inactive	Active	Inactive
Phytol	Active	Active	Inactive	Active	Inactive	Inactive

Table 6. The toxicity result of hit phytocompounds using Protox II server

Compounds	Immuno-toxicity	Mutageni-city	Cyto-toxicity	Eco-toxicity	Clinical toxicity	Nutritional toxicity
Serylserine	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Palmitic Acid	Inactive	Inactive	Inactive	Active	Inactive	Inactive
Benzenecarboximidothioic acid, N-phenyl-, 4-nitrophenyl ester	Inactive	Active	Inactive	Active	Inactive	Inactive
D-Allose	Inactive	Inactive	Inactive	Inactive	Inactive	Inactive
Pirenzepine	Inactive	Active	Inactive	Active	Inactive	Inactive
4-O-Methylmannose	Inactive	Active	Inactive	Active	Inactive	Inactive
Phytol	Active	Inactive	Inactive	Inactive	Inactive	Inactive

Conclusion

Through the application of Computer-Aided Drug Design (CADD), this extensive study has shed light on the potential medicinal uses of *Blighia sapida* (Ackee) phytochemicals for the treatment of hypertension, by identifying important *Blighia sapida* phytocompounds that exhibit minimal potential against critical protein targets involved in hypertension through docking computations and pharmacokinetic screening. Among the compounds present in *Blighia sapida*, Serylserine and Pirenzepine have the strongest potential in binding with protein target involved in hypertension. The pharmacokinetic assessments further reinforced the potential of these compounds, both Serylserine and Pirenzepine exhibited excellent profiles in terms of absorption, distribution, metabolism, and excretion (ADME). Notably, D-Allose also showed exceptional qualities, especially with regard to renal clearance and bioavailability, which makes it a viable option for more research and development.

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