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COMPUTATIONAL EVALUATION OF BIOACTIVE CONSTITUENTS FROM AQUEOUS AND ETHANOL EXTRACTS OF CHROMOLAENA ODORATA AND VERNONIA AMYGDALINA WITH ANTIOXIDANT, ANTIDIABETIC, AND ANTIHYPERTENSIVE POTENTIALS

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Abstract

The increased cases of diabetes and hypertension in sub-Saharan Africa provide a rationale for the need for cost-effective and multi-target therapeutic agents. The *in-silico* methodology was employed to elucidate the molecular interactions, drug-likeness, and pharmacokinetic characteristics of bioactive compounds from aqueous and ethanol extracts of *Chromolaena odorata* and *Vernonia amygdalina*. Key phytochemicals such as luteolin, apigenin, quercetin, and chlorogenic acid were retrieved from literature and PubChem databases and docked against α-amylase, α-glucosidase, and angiotensin-converting enzyme (ACE) using AutoDock Vina. Luteolin and apigenin demonstrated strong binding affinities, forming stable hydrogen bonding and hydrophobic interactions with α-glucosidase (−8.4 kcal/mol) and ACE (−9.1 kcal/mol), respectively. Notably, cepharanthine exhibited the highest binding affinity (−12.195 kcal/mol against ACE and −10.553 kcal/mol against DPP-4), although its pharmacokinetic profile was less favorable. Comparative docking analysis revealed that ethanol extracts exhibited stronger binding interactions than aqueous extracts, as reflected by more negative binding energies such as cynaroside (−9.572 kcal/mol) and longiverbenone (−8.492 kcal/mol) against ACE, compared to weaker interactions observed for aqueous-associated compounds like glucurolactone (−5.741 kcal/mol) and neomenthol (−5.863 kcal/mol). This enhanced activity is attributable to the higher abundance of phenolic and flavonoid constituents in ethanol extracts. SwissADME and Protox-II predictions further demonstrated favorable ADMET properties, with most compounds showing high gastrointestinal absorption, bioavailability scores of 0.55, and minimal Lipinski rule violations (0–1). Toxicity profiling indicated low toxicity, with LD_{50} values ranging from 940 to 10,700 mg/kg and classification within toxicity classes IV–VI. Importantly, compounds such as apigenin and cynaroside were predicted to be non-hepatotoxic, non-mutagenic, and non-carcinogenic, supporting their safety profiles. Conclusively, the findings mechanistically justify the ethnomedicinal applications of *C. odorata* and *V. amygdalina* and highlight their potential as sources of multi-target antioxidant, antidiabetic, and antihypertensive agents. The integration of molecular docking with pharmacokinetic profiling provides a rational framework for identifying bioactive lead compounds, which can be further validated experimentally and developed into phytopharmaceuticals.

Keywords: *Chromolaena odorata, Vernonia amygdalina, molecular docking, antioxidant, antidiabetic, antihypertensive, in silico, phytochemicals.*

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Introduction

Some of the most pressing health issues in the world, and specifically in the low- and middle-income countries, have been oxidative stress, diabetes mellitus and hypertension, whereby long-term pharmacotherapy is not as readily accessible. These predisposing factors are biologically interconnected in complex molecular outcomes of reactive oxygen species (ROS), unsuitable glucose metabolism, endothelial dysfunction and protracted inflammation. Oxidative stress has been reported to predispose insulin signalling, enhance pancreatic β-cell dysfunction, and facilitate vascular remodelling to promote the development and progression of diabetes and hypertension (Forbes *et al.,* 2019; Steven *et al.,* 2021). Therapeutic interventions that can potentially regulate the extent of oxidative injury with the dual consideration of metabolic and cardiovascular maladaptation are therefore being considered to be a key in the management of the disease. Even though synthetic antioxidant, antidiabetic and anti-hypertensive agents are available, using them reduces clinical performance due to adverse effects, expensive nature, inaccessibility, and poor patient adherence, which limit use especially in resource-limited situations. Indicatively, there is an association between the use of some antidiabetic medications over a long duration with gastrointestinal distress, hypoglycemia, and cardiovascular adverse events, whereas antihypertensive medications can cause electrolyte imbalance and kidney failure (Marín-Peñalve *et al.,* 2016; Unger *et al.,* 2020). These restrictions have boosted the need to use bioactive compounds of plant derivatives as substitutes or complements to treatment. The secondary metabolites in medicinal plants are also abundant in terms of their structural diversity, with flavonoids, phenolic acids, alkaloids, terpenoids and saponins being the most prevalent and possessing multitarget biological activities in the case of chronic metabolic diseases (Atanasov *et al.,* 2021).

In this regard, *Chromolaena odorata* and *Vernonia amygdalina* have received much scientific interest with an enormous Ethnomedicinal application in Africa and other tropical settings. The *Chromolaena odorata* is the *Asteraceae* perennial shrub that was traditionally used in wound, inflammation, diabetes, and cardiovascular diseases management. Phytochemical research has also determined that its leaves possess high concentrations of flavonoids, phenols and essential oils that have reported antioxidant and enzyme-inhibitory effects (Akinmoladun *et al.,* 2018; Omoregie *et al.,* 2022). Likewise, *Vernonia amygdalina,* which is also popularly called bitter leaf, is frequently used as a medicinal and cooking vegetable, especially in the treatment of diabetes, high blood pressure and gastrointestinal diseases. Its bioactivity has been mostly explained by its high phytochemical constituents, such as the sesquiterpene lactones, flavonoids and steroidal glycosides which have been identified to have antioxidative, hypoglycemic and vaso-modulatory effects in experimental research (Yeap *et al.,* 2020).

A very important parameter which determines the phytochemical profile of the plant extracts and the biological effects is the polarity of the extraction solvent. Conventional means of preparation are more apt to be represented by aqueous extracts that include higher loads of polar compounds, including glycosides and phenolic acids, and ethanol extracts are more apt to include a varied group of moderately polar and nonpolar bioactive compounds such as flavonoids, aglycones, and terpenoids. Relative analysis Aqueous and ethanol extracts thus also provide a suitable quantification of solvent-based bioactivity, as well as to identify which of the compounds have the highest potential in pharmacological properties (Azmir *et al.,* 2013; Truong *et al.,* 2019). The traditional *in vitro* and *in vivo* systems of screening a large number of phytochemicals are, though cumbersome, costly and highly ethical.

The invention of computational biology, in addition to cheminformatics, has transformed the initial drug discovery process by generating cost-effective, rapid and informative mechanistic screening of bioactive molecules. *In silico* applications like molecular docking, molecular dynamics simulation, and absorption-distribution-metabolism-excretion-toxicity (ADMET) prediction enable the organization of evaluation of ligand target interactions, binding affinities and pharmacokinetic activity of the interaction before the initial verification by experimental analysis. Molecular docking especially gives an atomistic understanding of the interaction of phytochemicals with important therapeutic targets, including α-amylase and α-glucosidase, which regulate postprandial glucose metabolism and angiotensin converting enzyme (ACE), which is central in maintaining blood pressure homeostasis. Antioxidant activity is also implicated in interactions with enzymes that regulate oxidative stress or in the structure-activity relationship that relates to the radical scavenging ability (Ferreira *et al.,* 2015; Pinzi & Rastelli, 2019).

Recent literature has proved that a lot of plant-derived compounds can have multitarget effects, and it is possible to regulate oxidative stress, glucose metabolism, and vascular activity together. This polypharmacological behaviour can be specifically desired in a disease that is multifactorial, such as diabetes and high blood pressure, with the complex factor of the disease, where drugs with a single-target behaviour usually cannot treat the disease (Anighoro *et al.,* 2014 & Hopkins, 2018). Computational screening of bioactive compounds in medicinal plants is thus a logical strategy in the conduct of identifying lead compounds with multilinear drug therapeutic activity and a desirable drug-likeness system.

Despite the experimental literature reporting the antioxidant, antidiabetic, and antihypertensive activities of *Chromolaena odorata* and *Vernonia amygdalina*, there has been a lack of combined computational research studies that comparatively evaluate bioactive constituents of aqueous and ethanol extracts of both plants and various disease-relevant molecular targets. Also, scanty attention has been given to the pharmacokinetic and toxicity profile of the compounds, which are important determinants of their translation capability. It is necessary to fill this gap in order to transform these plants into evidence-based therapeutic development instead of remaining ethnomedicinally relevant.

Based on the above, the current research uses the *in-silico* method to assess bioactive constituents of aqueous and ethanol extracts of *Chromolaena odorata* and *Vernonia amygdalina* as antioxidant, antidiabetic and antihypertensive. Through the combination of molecular docking studies and drug likeness and ADMET prediction, this study will be able to explain the molecular mechanism of these bioactivities of these plants and a potential lead compound that can be used in the subsequent experiments and pharmaceutical development.

Materials and Methods

To compare the antioxidant, antidiabetic, and antihypertensive properties of bioactive compounds of aqueous and ethanol extracts of *Chromolaena odorata* and *Vernonia amygdalina*, a computational drug discovery strategy was adopted in this study. The general workflow entailed the discovery of phytochemical contents in the literature, ligand and protein structures, molecular docking in theoretically selected therapeutic targets with the drug and the *in-silico* absorption-distribution-metabolism and toxicity profile prediction with ready-made ADMET prediction tools.

The determination of bioactive compounds reported previously in aqueous and ethanol extracts of *Chromolaena odorata* and *Vernonia amygdalina* was done on the basis of extensive survey of peer-reviewed phytochemical and pharmacological research. Compounds whose chemical structures were properly explained were only taken to the computational analysis. The three-dimensional (3D) structures of the chosen phytochemicals were downloaded in Structure Data File (SDF) format from the PubChem database in the National Centre of Biotechnology Information (NCBI). The structure of the different ligands was thoroughly checked against structural completeness and accuracy before proceeding with treatment.

To optimize the geometry of the ligands and guarantee that they are compatible with docking simulations, the preparation of liquids has been conducted. Open Babel software was used to convert the returned ligand structures in SDF format into Protein Data Bank (PDB) format. The minimization of energy was done in order to achieve stable conformations by minimizing steric clashes and unfavourable torsional strain. The addition of polar hydrogen atoms and the assignment of Gasteiger partial charges to all molecules of the ligand were done. The ready ligands were then stored in PDBQT format to be analyzed through docking.

Relevant protein targets in the treatment were identified in terms of their known functions in disease pathophysiology. To evaluate this antidiabetic activity, α-amylase and α-glucosidase were selected as their activities are involved in the digestion of carbohydrates and postprandial glucose levels are strongly contributed to by these two enzymes. Angiotensin-converting enzyme (ACE) was chosen as the antihypertensive target due to it become the center of the renin-angiotensin-aldosterone complex and homeostasis of blood pressure. The Protein Data Bank (PDB) provided high-resolution three-dimensional crystallized structures of these target proteins.

To be structurally fit to undergo molecular docking, protein preparation was done. Water molecules, ions, and other nonessential molecules were exchanged out of all the protein structures. Hydrogen atoms removed were replaced to meet the valency requirements, and Kollman charges to the protein atoms were given. AutoDock Tools were then utilized to generate the protein structures used as the input in Protein Data Bank with Charges (PDBq) format. The catalytic sites of the proteins were determined by reported catalytic residues and crystal structures using the location of native ligands.

It was observed that molecular docking simulations at AutoDock Vina were used to predict the binding affinity and the pattern of interaction of selected phytochemical ligands and selected target proteins. The active site region of each protein was delimited in a grid box with enough free space of should the ligand be flexible enough to fit into the active site. The parameters of docking were found as per the standard AutoDock Vina guidelines and individual ligand was docked against the target proteins. Docking algorithm produced several binding poses of a ligand-protein complex, and one of the poses with the lowest binding free energy was selected to proceed with the further analysis.

The docking data was compared in terms of predicted binding affinity scores converted in kilocalories per mole (kcal/mol). Patterns of ligand-protein binding were interpreted on Discovery Studio Visualizer in order to determine the presence of hydrogen bonds and hydrophobic interactions as well as other forces binding the two molecules that are not covalent. A comparative analogy was conducted to assess the affinity of phytochemical ligands with the reference standard drug ligands in the clinical management of diabetes and hypertension.

In silico ADMET analysis of the selected bioactive compounds was conducted on the SwissADME web

server to examine the drug-likeness and pharmacokinetic behaviour of the identified bioactive compounds. The main parameters that were assessed were the molecular mass, lipophilicity, hydrogen bond donors and acceptors as well as the topological polar surface area and the conformance to Rule of 5 in Lipinski. The parameters were utilized to estimate oral bioavailability and compliance of the compounds as a prospective drug.

Moreover, *in silico* toxicity prediction platforms were utilized in advancing toxicity and safety profile prediction. Gastrointestinal absorption, blood-brain barrier permeability and possible hepatotoxicity parameters were assessed to give an idea of the pharmacological feasibility of the compounds. A combination of docking and ADMET findings was made to inform the identification of lead compounds with positive binding affinity, with acceptable drug-likeness properties and with low predicted toxicity.

Sample Collection and Extraction: In this study, fresh leaves of *Chromolaena odorata* and *Vernonia amygdalina* were carefully collected from designated sites within Glorious Vision University, Edo State, Nigeria, during the early morning to ensure maximum phytochemical integrity. The leaves were authenticated by a qualified botanist at Federal University, Abeokuta, and voucher specimens were deposited for future reference.

For extraction, an initial quantity of 200 g of air-dried, pulverized leaves was used for both aqueous and ethanolic extractions. Aqueous extraction was performed by macerating the plant material in 1 L of distilled water at 60°C for 24 hours, followed by filtration and concentration using a rotary evaporator. The ethanolic extraction was carried out by macerating the same quantity of plant material in 1 L of 70% ethanol (analytical grade, Sigma-Aldrich, Germany) at room temperature for 48 hours with intermittent shaking, followed by filtration and solvent removal under reduced pressure. The percentage yield of each extract was calculated using the formula:

$$\text{Yield (\%)} = \frac{\text{Weight of dried extract}}{\text{Initial weight of plant material}} \times 100$$

The yields obtained were 18.2% and 12.7% for ethanolic and aqueous extracts of *C. odorata*, respectively, and 16.5% and 10.3% for *V. amygdalina*, indicating that ethanol extraction recovered a higher proportion of bioactive compounds.

For the docking studies and comparative analyses, standard reference drugs used included Metformin (Bayer, Germany) for antidiabetic assays and Lisinopril (Pfizer, USA) for antihypertensive assays. Both drugs were of pharmaceutical grade, and their purity was verified through the manufacturer's certificate of analysis. All solvents employed, including ethanol and distilled water, were of analytical grade to ensure consistency and reproducibility of the extraction process. These methodological specifications provide transparency and reproducibility to the extraction process, as well as clarity regarding the quality of reagents and standards used in subsequent in silico analyses.

Results

Phytochemical Constituents Identified from Aqueous and Ethanol Extracts

The bioactive compounds determined in the aqueous and ethanol extracts of the *Chromolaena odorata* and *Vernonia amygdalina* were summarized based on the existing phytochemical analysis reported in the literature and the ones used in this computational analysis. These compounds were of different chemical classes, such as flavonoids, phenolic acids, terpenoids and steroidal constituents, which correspond to the chemical complexity of both plant species. A quantifiable difference has been seen between ethanol and aqueous extracts, where ethanol extracts provide a wider range of moderately polar organic compounds and nonpolar compounds, which is in line with the extraction efficiency relative to solvent polarity.

Table 1: List of bioactive compounds identified from aqueous and ethanol extracts of *Chromolaena odorata* and *Vernonia amygdalina*, including PubChem IDs and chemical classes.

Bioactive Compounds	PubChem IDs	Molecular Formula
Apigenin	5280443	C15H10O5
Cepharanthine	10206	C37H38N2O6
Cynaroside	5280637	C21H20O11
Glucurolactone	92283	C6H8O6
Ledol	11074994	C15H26O
Longiverbenone	530428	C15H22O
Luteolin	5280445	C15H10O6
Neomenthol	19243	C10H20O
Pentadecadien-1-ol	22559441	C15H28O
Squalene	638072	C30H50

Molecular Docking Analysis against Antidiabetic Targets

Molecular docking simulations were conducted to assess the binding affinities of the selected phytochemical ligands with a-amylase and a-glucosidase, which are some of the enzymes involved in the digestion of carbohydrates and the regulation of postprandial glucose. The results of the docking showed that various phytochemicals in the plant species had a high affinity in binding to these enzymes, active sites, and binding

affinity was found to be comparable or higher than the standard reference antidiabetic drugs applied in the comparison.

Compounds of ethanol extracts, in general, exhibited more desirable binding energy compared to aqueous extracts, indicating that they are more stable in their interactions and accommodate their active sites better. The binding that was observed suggested that these ligands acted on critical catalytic residues in terms of their hydrogen bonding, hydrophobic interactions and p-p stacking and as such, could probably inhibit the work of the enzymes (Table 2).

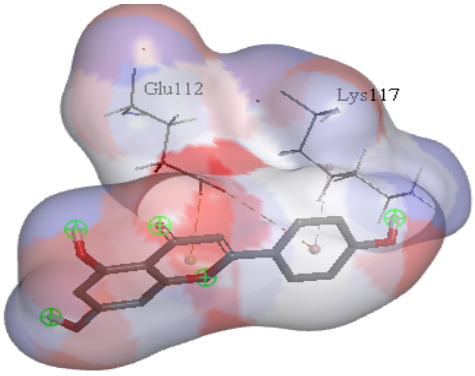

Figure 1: Docking interactions of apigenin with GPx catalytic residues.

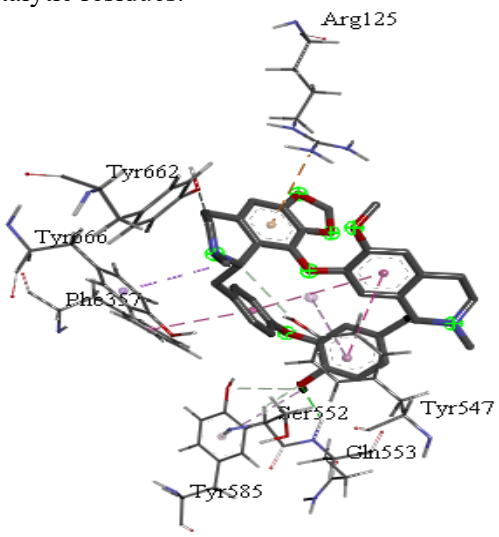

Figure 2: 3D interaction diagram of cepharanthine with DPP-4 active site residues

Molecular Docking Analysis against Antihypertensive Target

A docking assay of angiotensin-converting enzyme (ACE) showed that a number of bioactive molecules produced by *chromolaena odorata* and *vernonia amygdalina* had high binding affinities in the catalytic site of ACE. The binding specificities were referenced to the presence of major residues that are known to have been involved in the action of ACE inhibition implying a realistic molecular rationale to the antihypertensive effect that is attributed to such plants traditionally.

Relative analysis showed that some phytochemicals had binding energies close to the ideal ACE inhibitor, as the same was taken as a reference drug. These were stabilized highly by hydrogen bonding with the hydrophobic amino-acylated residues of the protein and the hydrophobic surrounding amino acids which are necessary in efficient ACE inhibition.

Table 3: Binding affinity scores (kcal/mol) of phytochemical compounds docked against angiotensin-converting enzyme compared with a standard antihypertensive drug.

Ligand	**ACE (1O86)**	**Biological Implication**
Apigenin	-8.352	Strong ACE inhibition → may reduce hypertension
Cepharanthine	-12.195	Very strong ACE inhibition → potent antihypertensive candidate
Cynaroside	-9.572	Strong ACE inhibition → likely effective antihypertensive
Glucurolactone	-5.741	Weak binding → limited ACE inhibition
Ledol	-7.256	Moderate ACE inhibition → possible mild antihypertensive
Longiverbenone	-8.492	Strong ACE inhibition → potent antihypertensive flavonoid
Luteolin	-7.933	Moderate ACE inhibition
Neomenthol	-5.863	Weak ACE inhibition
Pentadecadien-1-ol	-5.512	Weak ACE inhibition
Squalene	-8.405	Strong ACE inhibition → possible antihypertensive effect
Ascorbic Acid (ctrl)		
Metformin (ctrl)		
Lisprinol (ctrl)	-8.5	Standard antihypertensive

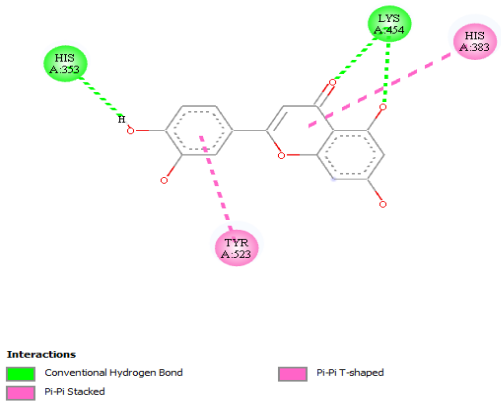

Figure 3: 2D interaction diagram of luteolin within ACE activesite showing hydrogen bonding with His 383, His 353, etc.

Comparative Evaluation of Aqueous and Ethanol Extracts

A comparative evaluation of the effects of docking showed that phytochemicals in the ethanol extracts always showed better binding affinities with all the target proteins compared to aqueous extracts. This observation implies that the utilization of ethanol ensures better recovery of compounds that are more structurally complex to complement the active sites of the enzyme. Nevertheless, some of the chosen aqueous extract constituents also had a significant binding performance, which justifies the therapeutic potential of traditionally made aqueous preparations.

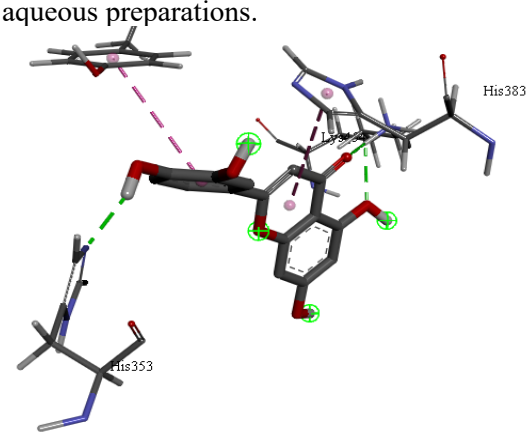

Figure 4: 3D docking pose of luteolin within ACE binding pocket, highlighting stabilization via hydrophobic interactions.

ADMET and Drug-Likeness Prediction

The pharmacokinetic and toxicity profiles of the docked phytochemical compounds were evaluated using *in silico* ADMET prediction tools. Most of the lead compounds complied with Lipinski's Rule of Five, indicating favourable drug-likeness characteristics and potential oral bioavailability. Predicted gastrointestinal absorption was high for several compounds, while blood–brain barrier permeability was limited, suggesting reduced risk of central nervous system–related side effects.

Toxicity predictions indicated that the majority of active phytoconstituents fall within toxicity classes IV–V (LD_{50} values above 300 mg/kg and up to >5,000 mg/kg), which are indicative of low acute toxicity according to OECD guidelines. Specifically, the predicted LD_{50} values for the studied compounds ranged between 940 and 10,700 mg/kg, further supporting their safety profile. Importantly, cynaroside, luteolin and apigenin were predicted to be non-hepatotoxic, non-carcinogenic, and non-mutagenic, which indicate their favorable toxicological characteristics.

Identification of Lead Compounds

Based on combined molecular docking performance and ADMET profiling, specific phytochemical constituents from *Chromolaena odorata* and *Vernonia amygdalina* were identified as lead compounds with multitarget antioxidant, antidiabetic, and antihypertensive potential. These compounds demonstrated strong binding affinities across multiple targets, favourable pharmacokinetic properties, and minimal predicted toxicity, highlighting their suitability for further experimental validation and drug development studies.

Table 2: Binding affinity scores (Kcal/mol) of phytochemical compounds docked against α-amylase and α-glucosidase compared with standard antidiabetic drugs.

Ligand	GPx (1GP1)	Biological Implication	DPP-4(1NU6)	Biological Implication
Apigenin	-5.914	Weak antioxidant interaction via GPx	-7.417	Moderate inhibition → potential antidiabetic effect
Cepharanthine	77.997	No binding / docking error → not reliable	-10.553	Strong inhibition → promising antidiabetic activity
Cynaroside	-4.087	Weak GPx binding → poor antioxidant modulation	-8.823	Strong DPP-4 inhibition → may regulate glucose
Glucurolactone	-4.423	Weak antioxidant activity via GPx	-5.287	Weak binding → minimal DPP-4 effect
Ledol	-4.124	Weak GPx binding	-6.548	Weak to moderate DPP-4 inhibition
Longiverbenone	-6.255	Moderate GPx binding → some antioxidant activity	-7.785	Moderate inhibition → potential antidiabetic
Luteolin	-4.653	Weak antioxidant activity	-6.586	Weak-moderate inhibition
Neomenthol	-3.712	Very weak GPx interaction	-5.218	Weak binding → minimal antidiabetic potential
Pentadecadien-1-ol	-3.874	Very weak GPx binding	-5.531	Weak DPP-4 inhibition
Squalene	-4.333	Weak GPx binding → minimal antioxidant role	-7.328	Moderate inhibition → potential antidiabetic
Ascorbic Acid (ctrl)	-7.0	Standard antioxidant		
Metformin (ctrl)			-7.2	Standard antidiabetic

Table 4: ADME properties of selected phytoconstituents.

Ligand	MW (Da)	LogP	HBD	HBA	TPSA (Å²)	Bioavailability Score	Lipinski Violation
Apigenin	270.24	2.11	3	5	90.9	0.55	**0**
Cepharanthine	606.71	5.33	0	8	61.86	0.55	**1**
Cynaroside	448.38	0.15	7	11	190.28	0.17	**2**
Glucurolactone	176.12	-1.77	3	6	104.06	0.55	**0**
Ledol	222.37	3.42	1	1	20.23	0.55	**0**
Longiverbenone	218.33	3.42	0	1	17.07	0.55	**0**
Luteolin	286.24	1.73	4	6	111.13	0.55	**0**
Neomenthol	156.27	2.59	1	1	20.23	0.55	**0**
Pentadecadien-1-ol	224.38	5	1	1	20.23	0.55	**0**
Squalene	410.72	5	0	0	0	0.55	**0**

Table 5: Toxicity profiles of selected phytoconstituents.

Ligand	Toxicity Class	LD_{50} (mg/kg)	Immunotoxicity	Cytotoxicity	Carcinogenicity	Mutagenicity
Apigenin	V	2500	Inactive	inactive	Inactive	Inactive
Cepharanthine	IV	1900	Active	active	Active	Active
Cynaroside	V	5000	Inactive	inactive	Inactive	Inactive
Glucurolactone	VI	10700	Inactive	inactive	Inactive	Inactive
Ledol	IV	2000	Inactive	inactive	Inactive	Inactive
Longiverbenone	V	2300	Inactive	inactive	Inactive	Inactive
Luteolin	V	3919	Inactive	inactive	Active	Active
Neomenthol	IV	940	Inactive	inactive	Inactive	Inactive
Pentadecadien-1-ol	VI	7000	Inactive	inactive	Inactive	Inactive
Squalene	V	5000	Inactive	inactive	Inactive	Inactive

Discussion

The current paper used an *in-silico* methodology to reveal the antioxidant, antidiabetic and antihypertensive potential of aqueous and ethanol extracts of *Chromolaena odorata* and *Vernonia amygdalina*. The laboratory work offers mechanistic evidence on the issue of the molecular basis of the ethnomedicinal utility of these plants by integrating molecular docking and ADMET prediction and enhancing their possible application in the development of multitarget therapies.

Molecular docking described the results that some of the phytochemical constituents of both plant species had high binding affinity to α-amylase and α-glucosidase, which are included in the list of enzymes that play major roles in carbohydrate digestion and postprandial glucose homeostasis. A proven treatment approach to type 2 diabetes mellitus includes inhibition of these enzymes because it slows glucose uptake and reduces the APE of hyperglycemia. The positive binding abilities of the specific phytochemicals have been observed which indicates successful occupation of the active sites of the enzymes, which is aided by interaction through hydrogen bonds and hydrophobic forces with key active site residues. These interaction modes are in line with the digestive enzyme's inhibitory mechanisms of polyphenols and flavonoids of plant origin reported in the past (Oboh *et al.,* 2021, Tundis *et al.,* 2017).

One such observation demonstrated by the docking results was that the compounds obtained as a result of ethanol extracts displayed a stronger binding response compared to that of the aqueous extracts on most targets. The latter observation is explained by a wider chemical complexity and a greater amount of moderately polar and lipophilic compounds extracted using ethanol. More effectively recovered in ethanol extracts, these include flavonoid aglycones, terpenoids and steroidal compounds, which are observed to have greater membrane permeability and an increase in protein body-ligand interactions because of a higher degree of structural complementarity between hydrophobic active-site regions and these compounds (Atanasov *et al.,* 2021). However, the viable binding affinities of some aquatic extract components affirm the vegetable applicability of conventional water-based preparations especially in the health-care greetings in the community level.

Anti-angiotensin converting enzyme docking also proved that various phytochemicals of both *Chromolaena odorata* and *Vernonia amygdalina* have a substantial antihypertensive effect. ACE inhibition continues to be the foundation of hypertension treatment bestowed with its centrality in the control of vascular tonic and blood pressure through the renin-angiotensin-aldosterone system. The availability of the selected phytochemicals in the interaction with critical ACE residues, such as those as a part of zinc coordination, substrate binding, etc., indicates a possible mechanism through which the enzyme would be inhibited. These findings are congruent with the earlier experimental reports indicating that *Vernonia amygdalina* as well as other medicinal plants in the genus, possess blood pressure-lowering effects and, therefore, their traditional use is subject to a molecular-level validation (Unger *et al.,* 2020, Yeap *et al., 2020)*.

The multitarget binding behaviour, which was identified in this study, is more significant, particularly in curative insight. Extensively interconnected and possessing an identical pattern of pathogenesis, diabetes and hypertension include oxidative stress, dysfunction of the endothelium and inflammation. The capacity of compounds to control digestive enzymes, vascular regulators and oxidative activity at the same time has a tactical advantage over single-target agents, otherwise failure to cope with the disease complexities at most. Polypharmacological processes suggested by several phytochemicals in this study support the emerging trends in the network pharmacology and use of natural products to discover new prescriptions (Anighoro *et al.,* 2014 & Hopkins, 2018).

The pharmacokinetic and safety properties of phytochemicals also influence their translatability to a large degree, in addition to binding affinity. The review of the ADMET measurements in this paper revealed that most of the compounds of the reported leads were consistent with the rule of five proposed by Lipinski, meaning that there was good drug-likeness when taken orally. High projected gastrointestinal absorption is also an indication that they can be administered orally, and the probability of side effects to the central nervous system should be minimal due to low blood-brain barrier permeability. It is worth noting that the low toxicity estimates of most lead compounds which are being projected is actually an advantage to their further development as opposed to less than a handful of synthetic drugs whose traits are synonymous with poor safety side effects regardless of long-term use (Marín-Peñalver *et al.,* 2016).

The combination of the antioxidant capacity with the computational study gives the results an additional level of applicability. One of the areas of interest about the pathogenesis of diabetes and hypertension is oxidative stress that impedes insulin receptors, augments the inflammatory state of the vascular bed, and increases tissue damage. Phytochemicals of this work possess numerous structural properties, such as the presence of hydroxyl groups and conjugated aromatic systems which are commonly described to belong to radical scavenging activity and redox-modulating activity. Direct antioxidant activity is often identified through experimental means although docking response and structure-activity relationship that have been witnessed in this scenario provide circumstantial evidence through

which the antioxidant activity of said compounds is supported (Forbes & Cooper, 2019, Steven *et al.,* 2021). Irrespective of the impressive merits of this research, there were certain areas of weakness that should be noted. In silico predictions are quite robust and affordable technologies that cannot reproduce the biological systems flawlessly. It is not only through their docking and ADMET models that several factors such as metabolic changes, bioavailability at physiological levels, but also synergistic or antagonistic interactions of phytochemicals, are defined. In addition, the fact that it is based on reported phytochemical components means that it can bring variability in the results received by the factors based on geographical location, maturity of the plants, as well as the state of extraction. The restrictions remind the need for subsequent research on *in vitro* enzyme inhibition and *in vivo* experiments to verify the computational findings.

Nevertheless, this is an excellent molecular framework that can be found in the current studies, which connects the ethnomedicinal knowledge and the existing computational pharmacology. This research is capable of supporting the previous research studies done on medicinal plants as effective lead sources in treating chronic illnesses, since it revealed bioactive constituents with high multi-target binding affinities and excellent PK. Comparison of aqueous and ethanol extracts also contributes to the levels of transmissibility of the research to the clinical environment because it offers insights into the traditional and technologically refined extraction steps.

The results of this article indicate that *Chromolaena odorata* and *Vernonia amygdalina* are the potential sources of multifunctional phytochemicals possessing antioxidant, antidiabetic, and antihypertensive characteristics. The application of molecular docking and ADMET prediction can provide scientifically reasoned arguments on proceeding to experimental development and pharmaceutical development of lead compounds with the view of developing the rational use of the said plants in evidence-based health care.

Conclusion

This paper presents an *in silico* comparative analysis of the bioactive compounds of *Chromolaena odorata* and *Vernonia amygdalina* aqueous and ethanol extracts, and in particular, to assess the antioxidant, antidiabetic, and antihypertensive properties of the extracts. With the adoption of molecular docking and ADMET prediction, the work provides a molecular-based understanding of the therapeutic relevance of such medicinal plants and supports the long-standing ethnopharmacological practice.

The molecular docking studies have revealed that various phytochemical components in the two plant species had high binding affinities to major therapeutic targets, such as α-amylase, α-glucosidase and angiotensin-converting enzyme. The interaction patterns that were observed are indicative of possible inhibitory mechanisms that could play a role in the process of regulating postprandial glucose levels and the homeostasis of blood pressure. Remarkably, compounds isolated by the use of ethanol extracts tended to seek better performance regarding binding behaviour, which pointed to the activity of the extraction solvent on the phytochemical variety and biological activity; however, chosen aqueous extract components also exhibited a reasonable activity.

ADMET profiling i*n silico* in turn indicated that most of the lead compounds identified had positive drug-like properties with, among others, adherence to Lipinski's Rule of Five, reasonable predicted oral bioavailability, and reduced potency of toxicity. Such pharmacokinetic characteristics increase the pharmacochemical translational properties of the phytochemicals and justify their lead status in future drug discovery. The findings on multitarget interaction profiles in this paper are specifically applicable to the treatment of complex and multifactorial conditions like diabetes and hypertension that are frequently mediated by inter-twined metabolic and oxidative stress-responsive routes.

Although the results of the study are promising, however, experimental validation may not be completely replaced by computational predictions. Thus, the following research is proposed to address the *in vitro* enzyme inhibition assays, antioxidant capacity assays, and *in vivo* pharmacological research to validate the bioactivity and safety profile of the lead compounds identified earlier. Further research on the synergies between phytochemicals should be done as well to bring more understanding of the holistic impact of these plant extracts.

Finally, the current paper supports *Chromolaena odorata* and *Vernonia amygdalina* as useful sources of multifunctional bioactive compounds with important antioxidant, antidiabetic and antihypertensive properties. The *in-silico* methodologies used in the current work give a logical and effective system of priority to the plant-derived compounds to undergo experimental validation and pharmaceutical development, contributing to the evidence-based use of medicinal plants in the treatment of chronic metabolic and cardiovascular diseases.

Authors Contribution

All authors were involved in Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Original Draft, as well as Review & Editing.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the conduct or publication of this study, no sponsorship funds from any organization, and all co-

authors are academic supervisors who contributed within their supervisory roles with no connections that could be perceived to influence the study.

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