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(RESEARCH ARTICLE)

In silico docking and ADMET evaluation of bioactive compounds from *Phyllanthus niruri* and captopril as angiotensin-converting enzyme (ACE) inhibitors for hypertension management

Vishal Murlidhar Girbane *, Rasika Ramchandra Kedari and Rushikesh Achut Munde

Department of Pharmacy, TMV's Lokmanya Tilak Institute of Pharmaceutical Sciences Pune, India 411037.

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Abstract

This study explores the molecular docking and ADMET properties of bioactive compounds from *Phyllanthus niruri* and captopril in relation to ACE inhibition for managing hypertension. The five natural compounds, including rutin, gallocatechin, quercitrin, astragalin, and kaempferol, were evaluated for their binding affinities through docking analysis. The results demonstrated that these compounds exhibit strong binding energies, with rutin showing the highest affinity (-9.8 kcal/mol) compared to captopril (-5.5 kcal/mol). ADMET profiling revealed that the natural compounds, particularly rutin and kaempferol, possess favorable pharmacokinetic properties, including high GI absorption and low toxicity. Additionally, while captopril exhibited high protein binding and moderate clearance, the natural compounds presented lower toxicity across various parameters, such as hepatotoxicity and genotoxicity. Overall, these findings suggest that *Phyllanthus niruri* compounds could serve as promising natural alternatives to captopril for ACE inhibition, offering an improved safety profile and favorable drug-likeness properties.

Keywords: *Phyllanthus niruri*; ADMET properties; Docking; ACE inhibition; Hypertension

1. Introduction

Hypertension, commonly known as high blood pressure, is a prevalent condition that affects a significant portion of the global population. It is characterized by persistently elevated blood pressure levels, with systolic blood pressure exceeding 140 mm Hg or diastolic blood pressure above 90 mm Hg. This condition is a major risk factor for various cardiovascular diseases, including stroke, heart attack, and kidney failure. The renin-angiotensin system, which regulates blood pressure and fluid balance in the body, plays a crucial role in the pathophysiology of hypertension. At the core of RAS is the angiotensin-converting enzyme, which converts angiotensin I to the vasoconstrictor angiotensin II. This leads to increased vascular resistance and blood pressure. ACE also degrades bradykinin, a peptide that promotes vasodilation, further contributing to blood pressure elevation. For decades, ACE inhibitors have been the cornerstone of hypertension management. Captopril, one of the first synthetic ACE inhibitors, is widely used to block ACE activity, thereby lowering blood pressure. However, the use of synthetic ACE inhibitors is associated with several side effects, including dry cough, dizziness, and potential kidney dysfunction, limiting their long-term use. This has led to growing interest in exploring natural alternatives with fewer adverse effects.[3,4]

Phyllanthus niruri, a plant widely known for its medicinal properties, has gained attention for its potential role in managing hypertension. The plant is rich in bioactive compounds such as flavonoids, lignans, and glycosides, which are believed to exhibit multiple pharmacological activities, including antihypertensive effects. Among these compounds, Rutin, Gallocatechin, Quercitrin, Astragalin, and Kaempferol have shown promise in previous studies for their ability to modulate ACE activity.In this study, molecular docking techniques were employed to evaluate the potential of these five

* Corresponding author: Vishal Murlidhar Girbane.

natural compounds from Phyllanthus niruri in inhibiting ACE. Molecular docking is a computational method used to predict how molecules bind to a target protein—in this case, ACE. By simulating the interaction between each compound and the active site of ACE, the binding affinities, hydrogen bonding, and hydrophobic interactions were assessed. The findings were compared with the docking results of captopril, the synthetic ACE inhibitor, to determine whether these natural compounds could offer comparable or superior inhibition.[17] This research aims to identify the most potent natural ACE inhibitors and explore their potential as alternatives to synthetic drugs. By comparing the binding efficiency of natural compounds with captopril, the study seeks to contribute valuable insights into the development of safer, plant-based antihypertensive therapies. Furthermore, these findings could open the door to new therapeutic strategies for managing hypertension while minimizing the risk of side effects associated with conventional ACE inhibitors.[20]

Figure 1 Phyllanthus Niruri

1.1. Phyllanthus Niruri

Phyllanthus niruri, a small herb from the Euphorbiaceae family, is widely distributed across tropical regions and has a long history of use in traditional medicine systems, including Ayurveda, Traditional Chinese Medicine, and Indonesian Jamu. Known for its diverse medicinal properties, this plant is utilized to treat a range of ailments such as jaundice, liver diseases, kidney stones, diabetes, dysentery, and viral infections. Its therapeutic potential is largely attributed to the presence of various bioactive compounds, including flavonoids, alkaloids, tannins, triterpenes, lignans, and polyphenols, which contribute to its antiviral, antimicrobial, hepatoprotective, and anti-inflammatory effects. In addition to these properties, P. niruri has shown significant promise in managing kidney stones and gallstones by inhibiting crystal formation and promoting stone elimination.[1] It is also recognized for its role in managing conditions like hepatitis B, liver toxicity, and hyperglycemia. The plant's bioactive compounds, such as rutin, gallocatechin, kaempferol, and quercetin, possess antioxidant and anti-inflammatory activities that help reduce oxidative stress, which is often linked to chronic diseases. P. niruri is especially known for its flavonoids, which contribute to its ability to modulate immune responses and reduce inflammation. Researchers have also highlighted the plant's potential in treating viral infections, including its antiviral activity against the hepatitis B virus and HIV, with compounds like niruriside showing particular promise in inhibiting reverse transcriptase activity.[2] The plant's pharmacological profile includes not only antiviral and antimicrobial activities but also significant anticancer properties, particularly through its lignans and polyphenolic compounds. Phyllanthus niruri is also of interest for its diuretic properties, which aid in kidney and urinary tract health, and its ability to regulate blood sugar levels, making it valuable for the management of diabetes.[5,6] The presence of compounds like ellagitannins, which include geraniin, corilagin, and isocorilagin, further enhances the plant's therapeutic effectiveness in treating a variety of ailments. Overall, P. niruri's rich phytochemical composition and wide range of pharmacological activities make it a highly promising candidate for developing natural remedies. With growing interest in plant-derived medicines, especially in tropical countries, P. niruri stands out as a potent source for the development of drugs aimed at chronic diseases, offering a natural and effective alternative to synthetic treatments.[18,19]

1.2. Captopril

Captopril is an angiotensin-converting enzyme (ACE) inhibitor commonly used to treat high blood pressure (hypertension) and heart failure. It works by reducing the production of certain chemicals that constrict blood vessels, which helps blood flow more smoothly and allows the heart to pump blood more effectively. It is often prescribed alone or in combination with other medications for these conditions.[3,4,7] Additionally, captopril improves survival rates and reduces heart failure risk following heart attacks and is used to treat kidney disease caused by diabetes. This medication is typically taken in tablet form, usually on an empty stomach, one hour before meals, and may be prescribed two or

three times daily. It's important to take captopril consistently as directed, even when feeling well, to manage chronic conditions effectively.[7]

Captopril has several potential side effects, including dizziness, fatigue, a metallic taste, and in rare cases, serious reactions like swelling of the face or difficulty breathing. It is not recommended during pregnancy as it may harm the fetus, and caution is needed if the patient has conditions such as diabetes or kidney disease.[8,9] Additionally, captopril can interact with certain medications, such as NSAIDs and potassium supplements, which require special consideration during treatment. Regular monitoring of blood pressure is necessary to track the medication's effectiveness.[17]

1.3. Mechanism of Action

Captopril works by blocking the angiotensin-converting enzyme (ACE), which normally converts angiotensin I into angiotensin II, a hormone that narrows blood vessels and raises blood pressure. By inhibiting this process, captopril helps relax blood vessels, lowering blood pressure. Additionally, it increases the release of renin, which further supports the blood pressure-lowering effect. This action helps reduce the strain on the heart and improves blood flow, making captopril effective in treating high blood pressure and heart failure.[3,7]

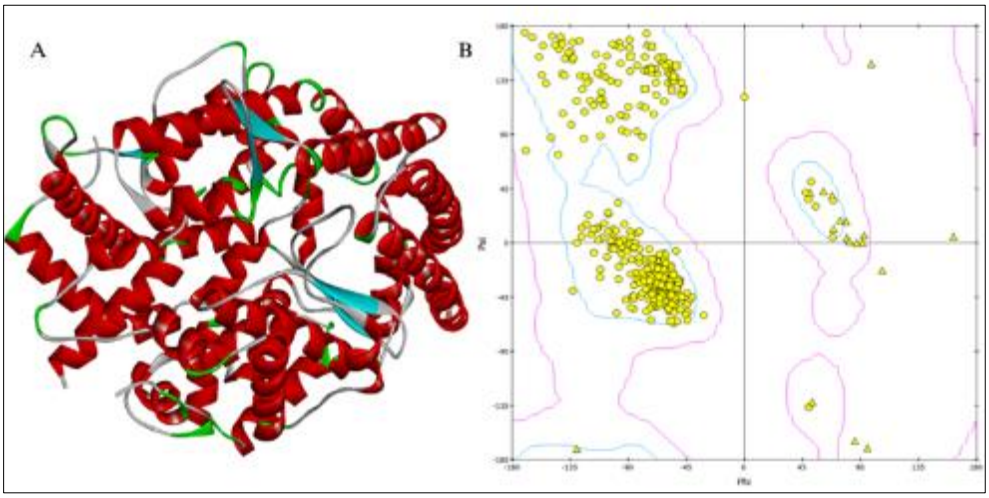

Figure 2 A) 3D Crystal Structure of angiotensin-converting enzyme (ACE), B) Ramachandran Plot of Protein Molecule

2. Material and methods

2.1. Ligand Preparation

The two-dimensional and three-dimensional structures of all six ligands were obtained from the PubChem chemical database, and the SMILES notation for each ligand was also collected. Each ligand was visualized using PyMOL and saved in PDB format. The ligands were then converted into PDBQT format using AutoDock Vina. The 2D images of the ligands are shown in the figure 3

2.2. Protein Preparation

The three-dimensional crystallographic structure of Angiotensin-Converting Enzyme (ACE) (PDB ID: 1O8A) was retrieved from the Protein Data Bank (www.rcsb.org). AutoDock Vina was used to remove water molecules, add polar hydrogen atoms, and assign Kollman charges to the protein. The protein structure was then visualized using a Ramachandran plot to analyze the phi and psi angles of the amino acid residues, as shown in the figure 2

2.3. Pharamacokinetics(ADME) and toxicology Predictions

ADME and Toxicology parameters of bioactive molecules aere predicted by online ADMET Lanb 3.0 and SWISS ADME soaftware tools.[16]

2.4. Ligand- Protein Docking

The molecular dockinf was performed using Autodock vina. The protein was added with polar hydrgen and kollman charge, ligand in pdbqt forrmed was introducted and a grid box was generated, then docking commands was given in

the command promopt and the outfile in pdbqt was generated. The output file was open in Discovery studio 2024 to identify the best pose of ligand based on the bindind energy. Finally, the pose having higest binding energy was selected to visualize the ligand-Protein interaction.[15]

The present study was conducted to assess the drug-likeness properties of phytoconstituents from *Phyllanthus niruri*. and their binding affinity with Angiotensin-Converting Enzyme (ACE). According to the Lipinski Rule of Five, compounds are likely to have poor absorption and bioavailability if their molecular weight exceeds 500 g/mol, if they have more than 5 hydrogen bond donors, a log P value greater than 5, or more than 10 hydrogen bond acceptors.

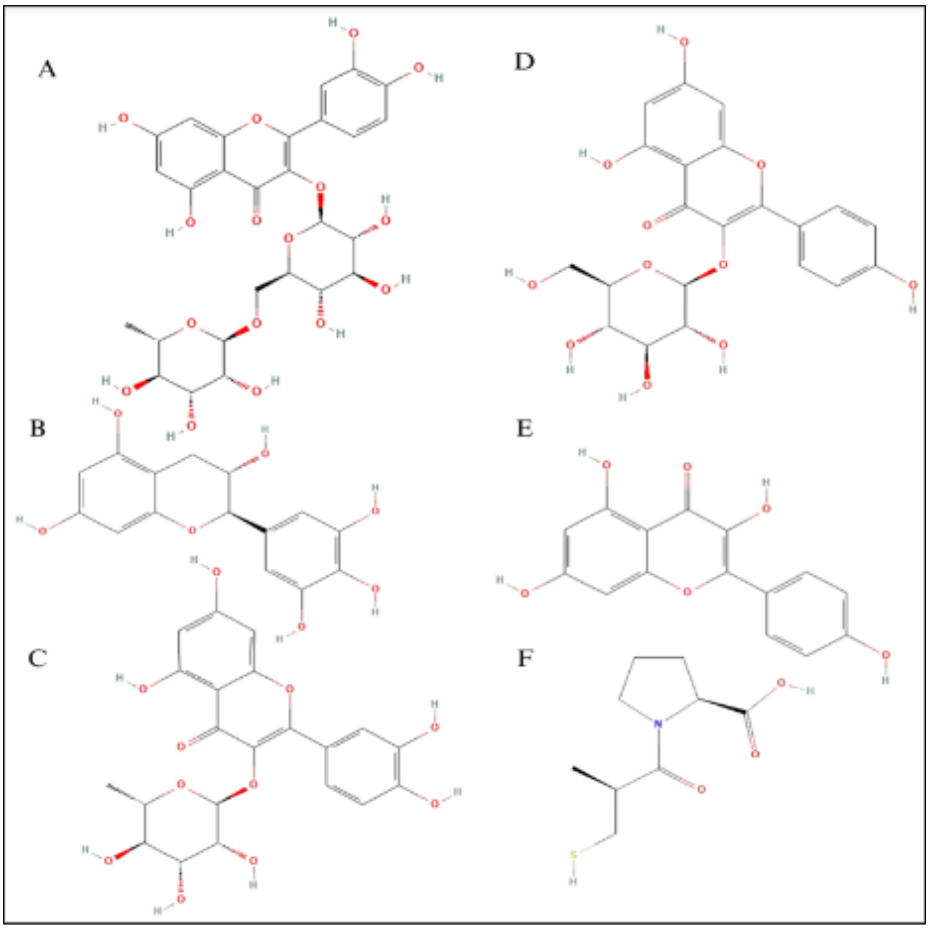

Figure 3 Chemical Structure of A) Rutin, B) Gallocatechin,C) Quercitrin, D) Astragalin, E) kaempferol, F) Captopril.10-14

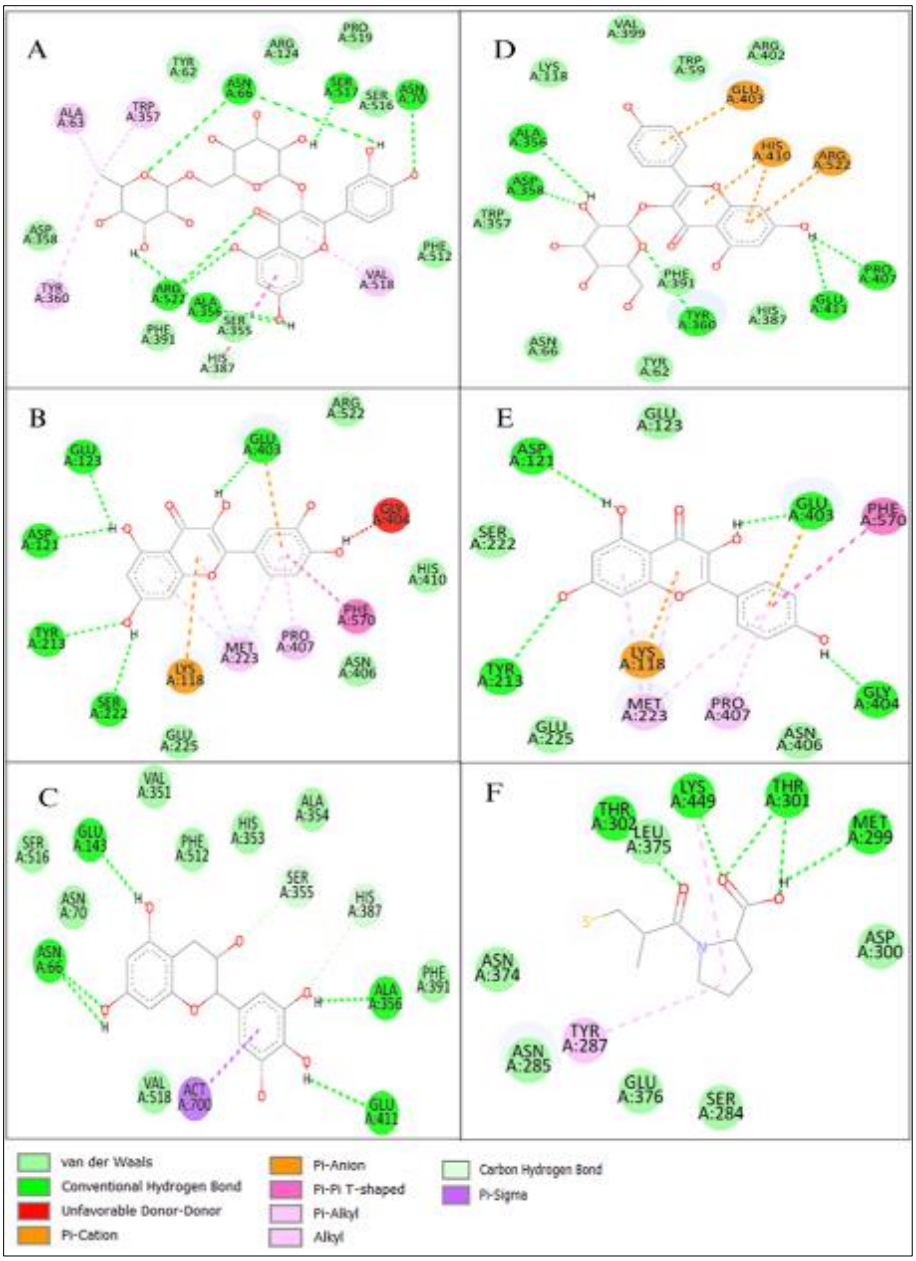

Figure 4 2D Protein Ligand Interaction of A) Rutin, B) Gallocatechin,C) Quercitrin, D) Astragalin, E) kaempferol, F) Captopril

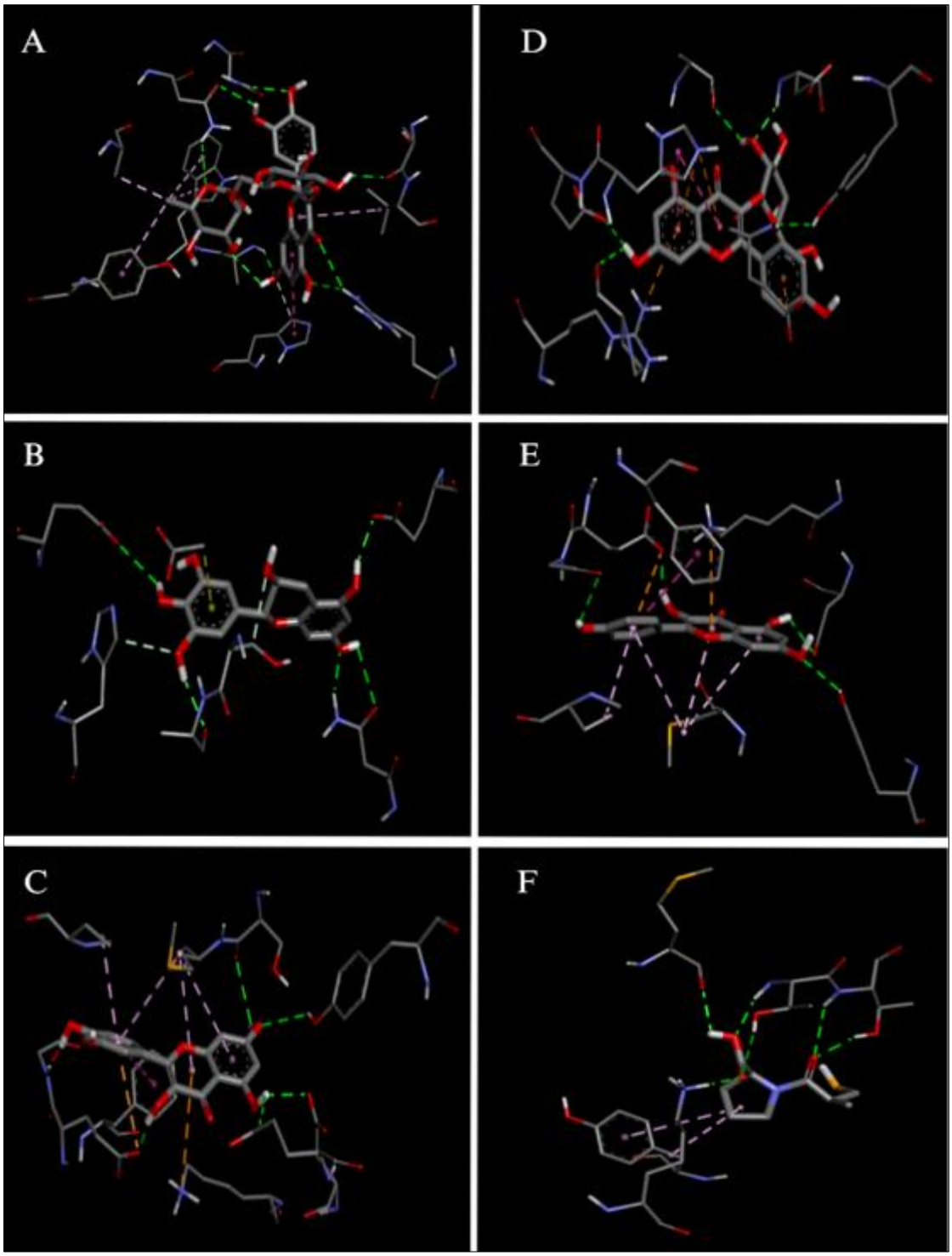

Figure 5 3D Protein Ligand Interaction of A) Rutin, B) Gallocatechin,C) Quercitrin, D) Astragalin, E) kaempferol, F) Captopril

3. Result and Discussion

The molecular docking analysis revealed that Rutin exhibited the highest binding energy (-9.8 kcal/mol) among all compounds, followed by Astragalin and Kaempferol (-8.8 kcal/mol each), Quercitrin (-8.6 kcal/mol), Gallocatechin (-7.6 kcal/mol), and the synthetic drug Captopril (-5.5 kcal/mol). These results suggest that natural compounds demonstrate stronger binding affinities to the ACE active site compared to Captopril, indicating their potential as effective inhibitors.

Table 1 Binding Energies of the compounds based on their rank (kcal/mol

Model	Rutin	Gallocatechin	Quercitrin	Astragalin	kaempferol	Captopril
	Binding Energies of the compounds based on their rank (kcal/mol)					
	A	B	C	D	E	F
1	-9.8	-7.6	-8.6	-8.8	-8.8	-5.5
2	-9.7	-7.6	-8.4	-8.5	-8.5	-5.4
3	-9.6	-7.6	-8.3	-8.5	-8.3	-5.1
4	-9.5	-7.4	-8.1	-8.4	-8.2	-5.1
5	-9.5	-7.4	-8.1	-8.3	-8.1	-5.0
6	-9.5	-7.3	-8.1	-8.3	-7.9	-4.9
7	-9.5	-7.3	-8.1	-8.3	-7.9	-4.9
8	-9.2	-7.2	-8.0	-8.2	-7.8	-4.8
9	-9.1	-7.2	-8.0	-8.0	-7.6	-4.8

In the medicinal chemistry evaluation, Gallocatechin, Kaempferol, and Captopril adhered to most drug-likeness rules, with Kaempferol and Captopril showing acceptance across Lipinski's, Pfizer's, Golden Triangle, and GSK rules. However, Rutin and other glycosides (Astragalin and Quercitrin) were largely rejected due to high molecular weights, excessive hydrogen bond donors/acceptors, or rule violations. Kaempferol had the best drug-likeness score among natural compounds (0.546), while Captopril had the highest overall score (0.682).

Table 2 Medicinal Chemistry Parameters ligand molecules

Parameter	Rutin	Gallocatechin	Quercitrin	Astragalin	kaempferol	Captopril
Lipinskies Rule	Rejected	Accepted	Rejected	Rejected	Accepted	Accepted
Pfizeres Rule	Accepted	Accepted	Accepted	Accepted	Accepted	Accepted
Golden Triangle	Rejected	Accepted	Accepted	Accepted	Accepted	Accepted
GSK Rule	Rejected	Accepted	Rejected	Rejected	Accepted	Accepted
Promiscuous Compound	0.582	0.358	0.86	0.666	0.928	0.481
Reactive Compound	0.146	0.521	0.223	0.268	0.728	0.397
SA Score	Easy	Easy	Easy	Easy	Easy	Easy

The absorption study indicated that Gallocatechin, Kaempferol, and Captopril demonstrated high gastrointestinal (GI) absorption, whereas Rutin, Astragalin, and Quercitrin had low GI absorption. All compounds showed poor permeability across Caco-2 and MDCK cells, with Rutin having the lowest skin permeation rate (-10.26 cm/s).

Table 3 Absorption Parameters of ligand Molecules

Parameter	Rutin	Gallocatechin	Quercitrin	Astragalin	kaempferol	Captopril
Caco-2 Permeability	-6.547	-6.436	-6.045	-6.347	-5.969	-4.831
MDCK Permeability	0.0	0.0	0.0	0.0	0.0	0.0
GI absorption	Low	High	Low	Low	High	High
Skin Permeation (LogKp)cm/s	-10.26	-8.17	-8.42	-8.52	-6.70	-7.38

In the distribution analysis, Kaempferol had the lowest volume of distribution (0.154 L/kg), indicating limited tissue distribution, while Captopril had the highest plasma free fraction (70.0%) and the lowest protein binding (31.7%), making it more bioavailable. None of the compounds were predicted to cross the blood-brain barrier (BBB).

Table 4 Distribution Parameters of ligand molecules

Parameter	Rutin	Gallocatechin	Quercitrin	Astragalin	kaempferol	Captopril
Fu (%)	14.7	21.2	12.9	12.7	1.4	70.0
BBB Permeant	No	No	No	No	No	No
PPB <90%.	85.0%	84.9%	86.1	85.1	97.9	31.7
VDss (L/Kg)	0.873	1.166	0.863	0.815	0.154	0.853

The metabolism evaluation revealed that Kaempferol was the only compound predicted to inhibit multiple cytochrome P450 (CYP) enzymes, including CYP1A2, CYP2D6, and CYP3A4, which could impact its metabolic stability and potential drug-drug interactions. Captopril and other natural compounds were not significant inhibitors of major CYP enzymes.

Table 5 Metabolism Parmeters of ligand molecules

Parameter	Rutin	Gallocatechin	Quercitrin	Astragalin	kaempferol	Captopril
CYP1A2 inhibitor	No	No	No	No	Yes	No
CYP2C19 inhibitor	No	No	No	No	No	No
CYP2C92 inhibitor	No	No	No	No	No	No
CYP2D6 inhibitor	No	No	No	No	Yes	No
CYP3A4 inhibitor	No	No	No	No	Yes	No

The excretion profile showed that Captopril had the fastest clearance (11.68 mL/min/kg) and the shortest half-life (1.022 hours), while Rutin had the slowest clearance (1.611 mL/min/kg) and the longest half-life (4.616 hours). This suggests that Captopril is rapidly eliminated, whereas Rutin may persist longer in the body.

Table 6 Excretion Parmeters of ligand molecules

Parameters	Rutin	Gallocatechin	Quercitrin	Astragalin	kaempferol	Captopril
Clearance (ml/min/kg)	1.611	12.148	3.602	2.893	5.696	11.68
T1/2 (Hr)	4.616	2.349	3.72	3.297	1.388	1.022

The toxicity study highlighted that most natural compounds demonstrated acceptable safety profiles, with lower probabilities of neurotoxicity, hematotoxicity, and nephrotoxicity compared to Captopril, which exhibited higher drug-induced toxicity risks. Kaempferol showed a higher risk of hepatotoxicity (0.844) than other natural compounds but was still within acceptable ranges.

In the drug-likeness evaluation, Captopril complied with all criteria, showing excellent drug-likeness (score 0.682). Kaempferol was the most promising natural compound, adhering to most drug-likeness rules (score 0.546). However, Rutin, Astragalin, and Quercitrin failed multiple criteria due to their high molecular weights and excessive hydrogen bond donors/acceptors.

Table 7 Toxicity Parmeters of ligand molecules

Parameters	Rutin	Gallocatechin	Quercitrin	Astragalin	kaempferol	Captopril
AMES Toxicity	0.756	0.538	0.751	0.837	0.546	0.434
Rat Oral Acute Toxicity	0.044	0.241	0.203	0.05	0.488	0.25
Carcinogenicity	0.047	0.216	0.1	0.354	0.716	0.079
Human Hepatotoxicity	0.406	0.484	0.438	0.625	0.389	0.844
Drug-induced Nephrotoxicity	0.148	0.016	0.068	0.108	0.019	0.993
Drug-induced Neurotoxicity	0.0	0.003	0.004	0.007	0.039	0.378
Hematotoxicity	0.023	0.015	0.054	0.054	0.045	0.868
Genotoxicity	0.868	0.982	0.946	0.981	0.977	0.996
Eye Irritation	0.905	0.992	0.983	0.862	0.998	0.488
Skin Sensitization	0.997	0.998	0.997	0.995	0.621	1.0
RPMI-8226 Immunitoxicity	0.098	0.009	0.072	0.054	0.040	0.026
hERG Blocker	0.008	0.102	0.017	0.018	0.069	0.004

Table 8 Drug likeness Score of Ligand Molecule's

Compound	Molecular Weight (g\mol)	Rotatable Bonds	Log P	No. of hydrogen bond donar	No. of hydrigen bond acceptor	Druglikness Score
	<500		<5	<5	<10	
Rutin	610.52	6	0.986	10	16	0.14
Gallocatechin	306.27	1	0.877	6	7	0.437
Quercitrin	448.38	3	1.315	7	11	0.276
Astragalin	448.38	4	1.044	7	11	0.279
kaempferol	286.24	1	1.965	4	6	0.546
Captopril	217.29	4	0.514	1	3	0.682

4. Conclusion

Based on the comprehensive analysis of molecular docking, ADMET properties, and toxicity profiles, several key insights emerge. Captopril demonstrated a stronger binding affinity to ACE than the natural compounds, but its pharmacokinetic properties (e.g., lower Caco-2 permeability and plasma protein binding) and toxicity profiles (e.g., hepatotoxicity, nephrotoxicity) suggest limitations in its therapeutic potential. On the other hand, Kaempferol, despite a slightly lower binding affinity, exhibited promising pharmacokinetics with high gastrointestinal absorption, favorable skin permeation, and a relatively safe toxicity profile, making it a potential lead compound for further exploration in treating hypertension. Rutin, Astragalin, and Quercitrin showed binding affinities similar to Kaempferol, but Rutin and Astragalin did not meet Lipinski's rule of five, suggesting limitations for oral bioavailability. Among the natural compounds, Gallocatechin had good ADMET properties and was well-absorbed, though its binding affinity was lower compared to others. In terms of toxicity, natural compounds generally exhibited lower risks, with Kaempferol emerging

as the most favorable, owing to its lower toxicity compared to Captopril. Thus, while Captopril remains a gold-standard drug for ACE inhibition, Kaempferol stands out as a promising natural alternative due to its acceptable binding affinity, favorable pharmacokinetics, and low toxicity profile, warranting further research for development.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed

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