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Studi *In Silico* Doking Molekuler Senyawa dari Meniran (*Phyllanthus niruri*) pada Reseptor Angiotensin Converting Enzyme (ACE) sebagai Agen Antihipertensi Potensial

In Silico Study Of Molecular Docking Of Compounds From Meniran (Phyllanthus Niruri) On Angiotensin Converting Enzyme (Ace) Receptor As Potential Antihypertensive Agents

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Abstrak

Hipertensi merupakan salah satu penyakit tidak menular utama dengan prevalensi yang terus meningkat dan menjadi penyebab utama mortalitas global. Angiotensin-Converting Enzyme (ACE) adalah target utama dalam terapi antihipertensi, di mana penghambatannya dapat membantu menurunkan tekanan darah. *Phyllanthus niruri*, yang dikenal dengan nama meniran, diketahui mengandung berbagai senyawa bioaktif dengan potensi sebagai agen antihipertensi alami. Penelitian ini bertujuan untuk mengevaluasi potensi 32 senyawa aktif dari *Phyllanthus niruri* sebagai kandidat inhibitor ACE melalui pendekatan *in silico* menggunakan Aturan Lima Lipinski (*Lipinski's Rule of Five*) dan doking molekuler. Struktur senyawa diperoleh dari basis data PubChem dan dinilai kelayakan farmasetisnya menggunakan aturan Lipinski. Doking molekuler dilakukan terhadap enzim ACE (PDB ID: 1J36) menggunakan AutoDock Vina, dengan lisinopril sebagai kontrol positif. Hasil penelitian menunjukkan bahwa 16 senyawa memenuhi seluruh kriteria Lipinski, sedangkan senyawa lainnya melanggar satu atau dua parameter. Analisis doking mengungkapkan bahwa 12 senyawa memiliki afinitas ikatan yang lebih kuat dibandingkan lisinopril (−10,3 kcal/mol), dengan rutin (−12,0 kcal/mol) dan fisetin 4′-glukosida (−11,8 kcal/mol) menunjukkan afinitas tertinggi. Temuan ini menunjukkan bahwa beberapa senyawa aktif dari *Phyllanthus niruri* memiliki potensi menjanjikan sebagai inhibitor ACE. Meskipun beberapa senyawa tidak sepenuhnya memenuhi aturan Lipinski, afinitas ikatan yang tinggi tetap menawarkan peluang signifikan untuk dikembangkan lebih lanjut sebagai agen antihipertensi oral alami.

Kata Kunci: *Phyllanthus niruri; Aturan Lima Lipinski; Doking Molekuler; ACE; Hipertensi; In Silico*

Abstract

Hypertension is one of the leading non-communicable diseases with increasing prevalence and is a major cause of global mortality. The Angiotensin-Converting Enzyme (ACE) is a primary target in antihypertensive therapy, where its inhibition can help lower blood pressure. Phyllanthus niruri, commonly known as meniran, is known to contain various bioactive compounds with potential as natural antihypertensive agents. This study aims to evaluate the potential of 32 active compounds from Phyllanthus niruri as ACE inhibitor candidates through an in silico approach using Lipinski's Rule of Five and molecular docking. The compound structures were obtained from the PubChem database and assessed for pharmaceutical feasibility using Lipinski's Rule. Molecular docking was performed against the ACE enzyme (PDB ID: 1J36) using AutoDock Vina, with lisinopril as the positive control. The results showed that 16 compounds fully met all Lipinski's criteria, while the remaining compounds violated one or two parameters. Docking analysis revealed that 12 compounds exhibited stronger binding affinity than lisinopril (−10.3 kcal/mol), with rutin (−12.0 kcal/mol) and fisetin 4′- glucoside (−11.8 kcal/mol) showing the highest affinities. These findings suggest that several active compounds from Phyllanthus niruri possess promising potential as ACE inhibitors. Although some compounds did not

fully comply with Lipinski's Rule, their high binding affinities still offer significant opportunities for further development as natural oral antihypertensive agents.
Keywords: *Phyllanthus niruri, Lipinski's Rule of Five, Molecular Docking, ACE, Hypertension, In Silico*.

BACKGROUND

Hypertension, or high blood pressure, is one of the most common chronic diseases in the general population and a leading cause of cardiovascular disorders such as stroke, kidney failure, and heart attack. According to data from the World Health Organization (WHO), more than 1 billion people worldwide suffer from hypertension, and its prevalence continues to rise each year. One of the main physiological mechanisms in blood pressure regulation is the Renin-Angiotensin-Aldosterone System (RAAS). Angiotensin-Converting Enzyme Inhibitors (ACEIs) work by inhibiting the formation of angiotensin II, which stimulates the synthesis and secretion of aldosterone, thereby increasing blood pressure through vasoconstriction (Rahmadani, 2019).

Although synthetic ACE inhibitors such as lisinopril are widely used, side effects such as dry cough electrolyte imbalances, and allergic reactions have prompted the search for safer natural alternatives. Medicinal plants like Phyllanthus niruri (commonly known as meniran) are well known in traditional medicine for their pharmacological activities, including diuretic, hepatoprotective, and antihypertensive effects. This plant contains various bioactive compounds such as flavonoids, tannins, and lignans, which are suspected to have ACE-inhibitory potential. However, scientific data explaining the molecular interactions between the active compounds of P. niruri and the ACE enzyme remain limited.

In the past decade, in silico approaches such as molecular docking have become essential methods in modern drug discovery. Molecular docking is a computational technique used to gain insights into drug development by predicting the interactions between ligands and receptors, along with their binding affinities. This method helps to shorten research time, reduce costs, and refine the scope of studies (Ayu Rahmania et al., 2022).

In addition to docking, Lipinski's Rule of Five is an important parameter for evaluating the drug- likeness of compounds as oral drug candidates, based on physicochemical properties such as molecular weight, logP, and the number of hydrogen bond donors and acceptors. It serves as a practical guideline to assess whether a chemical compound with certain pharmacological or biological activity is likely to be orally active in humans. By combining these two approaches, this study aims to evaluate 32 active compounds from Phyllanthus niruri against the ACE receptor target based on their pharmaceutical feasibility and molecular binding affinity, in order to identify potential candidates for natural product-based oral antihypertensive agents.

METHODS

This study employed an in silico approach to evaluate the potential of active compounds from Phyllanthus niruri as Angiotensin-Converting Enzyme (ACE) inhibitors. The research consisted of two main stages: (1) pharmaceutical feasibility analysis based on Lipinski's Rule of Five, and (2) molecular docking simulations between the compounds and the ACE receptor to assess binding affinity and interactions with active site residues.

Compound Collection and Preparation

A total of 32 active compounds from Phyllanthus niruri were identified through a review of scientific literature and confirmed in the KNApSAcK and PubChem databases. The 3D structures ofeach compound were downloaded in .SDF or .SMILES format from the website https://pubchem.n.bi.nlm.nih.gov.

Lipinski's Rule of Five Analysis

The drug-likeness of the compounds as potential oral drug candidates was evaluated based on Lipinski's Rule of Five, which includes four main criteria: molecular weight ≤ 500 Daltons, LogP ≤5 (a measure of lipophilicity), number of hydrogen bond donors (HBD) ≤ 5, and number of hydrogen bond acceptors (HBA) ≤ 10. The analysis was conducted using the SwissADME website (https://www.swissadme.ch/), a web-based pharmacokinetic prediction platform developed by the Swiss Institute of Bioinformatics. Each compound was input in SMILES format to evaluate the above parameters. Compounds with no more than one violation of Lipinski's criteria were still considered for further analysis.

Protein Structure Preparation

The three-dimensional structure of the target protein, Angiotensin-Converting Enzyme (ACE), wasobtained from the Protein Data Bank (https://www.rcsb.org/) with the PDB ID 1J36. This structure was selected because it contains a co-crystallized inhibitor ligand, which can serve as a reference for validation and identification of the active site. After downloading, the protein structure was processedusing AutoDock Tools (ADT). The protein preparation steps included removal of water molecules and the native ligand from the crystal structure, addition of polar hydrogen atoms to

optimize hydrogen bonding interactions, and assignment of partial charges using the Gasteiger method. The fully prepared protein structure was saved in .PDBQT format.

Docking Validation

Docking validation was performed through re-docking of the native ligand (lisinopril) into the active site of the ACE enzyme to ensure the reliability of the predicted binding pose and Root Mean Square Deviation (RMSD) value. An RMSD value of less than 2.0 Å was considered acceptable, indicating that the docking method is valid and capable of accurately reproducing the native ligand's binding conformation.

Molecular Docking

The docking of 32 test ligands to the target protein was carried out using the same procedure as the validation step, by applying the same grid box position and dimensions. The key parameters observed during the docking process included binding energy (ΔG), interacting amino acid residues, types of interactions, and bond distances. Lower binding energy indicates a more stable interaction between the ligand and receptor. The more stable the interaction, the greater the predicted biological activity of the ligand toward the target receptor.

Visualization and Interaction Analysis

Visualization of the docked ligand protein complexes was performed using BIOVIA Discovery Studio to examine the interactions between ligands and the protein, including the specific amino acid residues involved. Test ligands that interacted with amino acid residues and formed similar types of bonds as the native ligand were considered to have potential similarity in biological activity, due to the resemblance in binding interactions. This analysis served as an additional validation step to ensure that the binding was not only strong in terms of affinity, but also involved the catalytic residues accurately and specifically.

RESULT AND DISCUSSION

Lipinsky's Rule of Five Analysis

An initial evaluation of 32 active compounds from Phyllanthus niruri was conducted using Lipinski's Rule of Five parameters. These parameters are closely related to the physicochemical properties of compounds, such as solubility, membrane permeability, and distribution within the body. Compounds with high molecular weight generally have greater difficulty penetrating biological membranes and lower water solubility, which can reduce oral bioavailability (Syahputra, 2017). Meanwhile, the LogP value is used to assess compound lipophilicity—excessively high values (>5) increase the risk of fat accumulation and toxicity, whereas very low values indicate excessive hydrophilicity, which can hinder cell membrane penetration. Additionally, the number of hydrogen bond donors and acceptors influences the polarity of molecules; compounds with excessive hydrogen bonding tend to be overly polar and have difficulty crossing lipid membranes (Syahputra, 2017). Based on the analysis performed using SwissADME (https://www.swissadme.ch/), 16 out of the 32 compounds fully met all Lipinski criteria without any violations, indicating strong potential as oral drug candidates. The remaining compounds, although violating one or more rules, were still considered for further analysis due to their natural origin—natural compounds often possess complex structures while maintaining significant biological activity.

Table 1. Predicted Results of Lipinski's Rule of Five

No	Compound	MW (≤500 Da)	Log P (≤5	H-Bonds Donor (≤5)	H-Bonds Aksepto r (≤10)	Aqueous Solubility	Notes
1.	4-Methoxy norsecurinine	233.26	2.25	0	4	Soluble	Compliant
2	Astragalin	448.38	-0.25	7	11	Soluble	Not Compliant
3	Beta sitosterol	414.71	7.24	1	1	Poorly Soluble	Not Compliant
4	Catechin	290.27	1.33	5	6	Soluble	Compliant
5	Ellagic Acid	302.19	0.79	4	8	Soluble	Compliant
6	Epicatechin-3-O-gallate	442.37	1.30	7	10	Soluble	Not Compliant
7	Eriodictin	434.39	0.51	6	10	Soluble	Not Compliant
8	Fisetin 4'-glucoside	448.38	-0.14	5	10	Soluble	Compliant
9	Gallic Acid	170.12	0.21	4	5	Soluble	Compliant

10	Gallocatechin	306.27	1.47	6	7	Soluble	Not Compliant
11	Gallocatechin-3-O-gallate	458.37	1.73	8	11	Soluble	Not Compliant
12	Glucogallin	332.26	1.14	7	10	Soluble	Not Compliant
13	Hinokinin	354.35	3.08	0	6	Moderately Soluble	Compliant
14	Hirsutrin	464.38	2.11	8	12	Soluble	Not Compliant
15	Hypophyllanthin	430.49	4.27	0	7	Poorly Soluble	Compliant
16	Isoquercetin	464.38	0.94	8	12	Soluble	Not Compliant
17	Kaempferol 4'-rhamnoside	432.38	2.48	6	10	Soluble	Not Compliant
18	Kaempferol-3-O-rutinoside	594.52	0.79	9	15	Soluble	Not Compliant
19	Lintetralin	400.46	4.16	0	6	Poorly Soluble	Compliant
20	Luteolin 7-O-(2-apiosyl-6- malonyl)-Glucoside	666.54	1.70	9	18	Soluble	Not Compliant
21	Myricetin	318.24	1.08	6	8	Soluble	Not Compliant
22	Naringenin	272.25	1.75	3	5	Soluble	Compliant
23	Niranthin	432.51	4.44	0	7	Poorly Soluble	Compliant
24	Nirtetralin	430.49	4.03	0	7	Poorly Soluble	Compliant
25	Phyllanthin	418.52	4.25	0	6	Poorly Soluble	Compliant
26	Phyltetralin	416.51	4.10	0	6	Poorly Soluble	Compliant
27	Pinocembrin	256.25	2.11	2	4	Soluble	Compliant
28	Protocatechuic acid	154.12	0.66	3	4	Soluble	Compliant
29	Quercetin	302.24	1.63	5	7	Soluble	Compliant
30	Quercitol	164.16	0.77	5	5	Soluble	Compliant
31	Quercitrin	448.38	1.60	7	11	Soluble	Not Compliant
32	Rutin	410.52	0.46	5	10	Soluble	Compliant

Receptor and Ligand Preparation

The Angiotensin-Converting Enzyme (ACE) receptor with PDB ID 1J36 was obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank in .pdb format. The 3D structure of ACE and its co-crystallized native ligand are shown in Figure 1. Protein structures retrieved from the PDB typically contain solvents (such as water molecules) and other non-standard residues. During the preparation process, the original ligand and water molecules were removed to isolate the clean protein structur (Rachmania, 2019). The selected macromolecule, 1J36, was co- crystallized with a ligand and water molecules. These components must be removed because they may interfere with the docking process. The presence of water molecules can mediate interactions between the ligand and receptor, potentially affecting docking results. Likewise, the presence of the native ligand at the active site may hinder the binding of test ligands. Therefore, the macromolecule was cleaned by removing solvents, the native ligand, and non-standard residues using the Discovery Studio Visualizer program, resulting in a structure ready for further processing. The cleaned structure was saved in .pdb format. The native ligand, lisinopril, was also extracted from the macromolecular complex using Discovery Studio Visualizer and saved separately in .pdb format for use as a reference in the docking validation process.

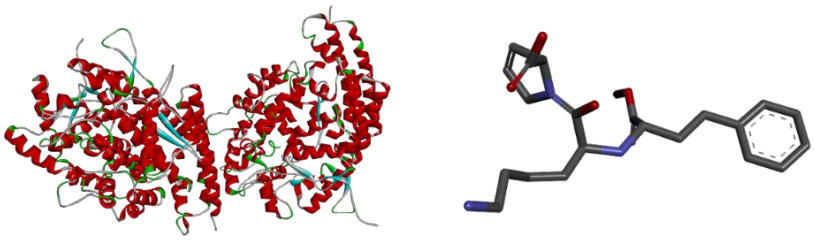

Figure 1. 3D structure of the ACE receptor without the ligand and the native ligand lisinopril
Docking Method Validation

The purpose of validating the molecular docking method is to ensure that the protocol used meets the required standards and can be reliably applied in subsequent screening processes. The main parameter used for validation is the Root Mean Square Deviation (RMSD). RMSD measures the deviation in the binding pose of the protein–ligand complex before and after docking, based on the crystal structure. A docking method is considered valid if the RMSD value is ≤ 2.0 Å (Hartanti et al., 2022). In this study, the RMSD value obtained from the validation process was 0.1207 Å, indicating that the docking method used is valid. The RMSD result is presented in Table 2. The closer the RMSD value is to zero, the more similar the docked ligand pose is to the native ligand, suggesting high accuracy of the docking protocol. This confirms that the developed protocol is acceptable and suitable for further use in virtual screening for potential new compounds (Siagian et al., 2022). The visualization of the validation pose between the native ligand (pink) and the docked ligand (silver) is shown in Figure 2, demonstrating that both molecules share a highly similar orientation and atomic alignment. In contrast, RMSD values greater than 2.0 Å would show significant differences in the position and angle of the two molecules, even if the number of atoms is the same.

Table 2. Re-docking Validation Results Using Lisinopril

PDB ID	Grid Box Coordinates (x, y, z)	RMSD Cluster (A)	RMSD Reference (A)	Binding Energy (kkal/mol)
1J36	21.127 2.4 49.115	0,1207	≤ 2	-10.3

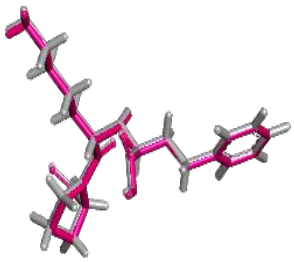

Figure 2. Visualization of docking validation between the native ligand lisinopril (pink) and the redocked ligand (silver)

Molecular Docking

Based on the molecular docking results, the binding energy values of the test compounds ranged from -5.6 kcal/mol to -12.0 kcal/mol. Among all tested compounds, rutin exhibited the most favorable binding energy. When compared to the standard drug lisinopril, which had a binding energy of -10.3 kcal/mol, several compounds—namely β-sitosterol, epicatechin-3-O-gallate, fisetin 4'-glucoside, hirsutrin, isoquercetin, and kaempferol 4'-rhamnoside—showed even lower (more negative) binding energies. These results suggest that several compounds found in Phyllanthus niruri (Meniran) possess potential as antihypertensive agents. The negative binding energy values indicate that the interactions are thermodynamically favorable and occur spontaneously, thereby allowing stable ligand-receptor binding with the angiotensin-converting enzyme (ACE). The ΔG value reflects the amount of energy released

upon interaction or bond formation with the target receptor; the more negative the value, the stronger the interaction due to greater energy expenditure in bond formation (Kelutur & Mustarichie, 2020).

Table 3. Docking Result of Compounds

No	Compound	Binding Energy (kkal/mol)	Hydrogen Bond	Bond Distance (A)
1.	Native Ligand Lisinopril	-10.3	TYR113 (Akseptor)	3,22641
			ARG51 (Donor)	4,79437
			LYS62 (Donor)	4,2993
			LEU120 (Donor)	4,28133
2.	4-Methoxy norsecurinine	-7.3	GLN266 (Akseptor)	3,32877
			HIS367 (Akseptor)	5,22647
3.	Astragalin	-8.1	HIS394 (Akseptor)	5,75213
4.	Beta sitosterol	-10.6	SER121 (Donor)	3,30003
			LEU120 (Donor)	4,3407
			TYR105 (Donor)	4,773
			ALA106 (Donor	4,56827
5.	Catechin	-8.8	LYS438 (Donor)	2,93282
6.	Ellagic Acid	-7.9	THR364 (Akseptor)	3,05455
			GLU368 (Akseptor)	3,99742
			ALA338 (Akseptor)	5,25702
7.	Epicatechin-3-O-gallate	-11.5	ALA338 (Akseptor)	5,7303
8.	Eriodictin	-9.8	-	-
9	Fisetin 4'-glucoside	-11.9	TYR113 (Akseptor)	2,82198
			ASP360 (Akseptor)	2,22705
			HIS371 (Akseptor)	2,20072
			GLU395 (Akseptor)	2,33657
			HIS337 (Akseptor)	4,84511
			VAL504 (Akseptor)	4,47747
10	Gallic Acid	-6.0	LYS438 (Donor)	3,6111
			ASP399 (Akseptor)	4,51914
11	Gallocatechin	-9.6	THR364 (Akseptor)	2,69664
			SER402 (Akseptor)	2,94949
			LYS62 (Donor)	3,20959
			ASP399 (Akseptor)	4,22403
			GLN266 (Akseptor)	2,20767
			PHE363 (Akseptor)	2,37661
12	Gallocatechin-3-O-gallate	-8.8	ASP360 (Akseptor)	3,55427
13	Glucogallin	-9.4	ASP399 (Akseptor)	2,17201
			ASP437 (Akseptor)	2,17552
			LYS62 (Donor)	4,03513
			SER402 (Akseptor)	3,54866
			PHE363 (Donor)	5,28669
			THR364 (Donor)	3,48858
14	Hinokinin	-8.2	LYS438 (Donor)	3,03908
15	Hirsutrin	-11.6	ASP360 (Akseptor)	3,7415
			ASN261 (Donor)	3,38897
			THR364 (Donor)	4,0592
			HIS367 (Donor)	5,63092
			ASP399 (Akseptor)	2,59008
			HIS337 (Akseptor)	3,42434
			ALA338 (Akseptor)	1,82445
			HIS497 (Akseptor)	2,52556
			TYR113 (Akseptor)	2,99588
16	Hypophyllanthin	-6.8	TRP341 (Donor)	4,72533

				4,98218
				5,06658
				5,07301
17	Isoquercetin	-11.5	ASP437 (Akseptor)	2,35122
			THR365 (Donor)	3,91568
			ASP360 (Akseptor)	3,64385
			TYR113 (Akseptor)	2,47338
			GLU150 (Akseptor)	2,08693
18	Kaempferol 4'-rhamnoside	-10.1	-	-
19	Kaempferol-3-O-rutinoside	-11.6	THR44 (Donor)	2,72762
			TRP341 (Donor	2,43628
				4,96082
20	Lintetralin	-9.0	ASP342 (Donor)	3,2904
			TRP341 (Akseptor)	3,4054
			TYR496 (Donor)	3,49661
			GLU368 (Akseptor)	3,4811
			THR387 (Donor)	3,60894
			PRO391 (Donor)	3,79363
			ARG51 (Donor)	3,70178
			HIS371 (Donor)	3,70178
21	Luteolin 7-O-(2-apiosyl-6-malonyl)-glucoside	-9.8	-	-
22	Myricetin	-9.9	THR364 (Donor)	2,70713
			HIS337 (Akseptor)	3,48639
			SER402 (Donor)	3,38232
			ASP399 (Akseptor)	4,81333
			GLN265 (Donor)	3,97133
23	Naringenin	-9.5	THR364 (Donor)	2,98789
			LYS62 (Donor)	3,18181
			ASP399 (Akseptor)	4,47397
			PHE363 (Akseptor)	4,11318
			HIS367 (Donor)	4,83006
24	Niranthin	-6.5	ARG506 (Donor)	4,99078
			VAL502 (Donor)	4,75285
25	Nirtetralin	-9.1	GLU503 (Donor)	3,66245
			ALA203 (Donor)	4,42505
			TRP204 (Donor)	5,19076
26	Phyllanthin	-5.6	ASP342 (Akseptor)	3,53184
			TYR344 (Akseptor)	4,89563
27	Phyltetralin	-8.3	THR387 (Donor)	3,39741
			HIS371 (Akseptor)	4,53341
			TRP341 (Donor)	4,73457
28	Pinocembrin	-8.1	HIS367 (Donor)	4,65839
29	Protocatechuic acid	-6.9	THR434 (Donor)	3,18143\
			SER406 (Donor)	2,21847
			SER402 (Donor)	3,36513
			LYS438 (Donor)	4,19745
			PHE363 (Akseptor)	4,18274
30	Quercetin	-8.5	-	-
31	Quercitol	-6.5	THR364 (Akseptor)	2,84666
			PHE363 (Akseptor)	2,53857
			ASP260 (Akseptor)	3,08039
			GLN266 (Akseptor)	2,68266
32	Quercitrin	-9.3	HIS367 (Donor)	5,3118
33	Rutin	-12.0	THR44 (Donor)	2,9444

THR387 (Donor)	3,16514
TYR113 (Akseptor)	3,01588
TYR344 (Donor)	2,5597
ASP342 (Akseptor)	2,48249

Visualization and interaction analysis

Visualization and interaction analysis of the docking results were conducted to observe the binding interactions between both the reference ligand and the test ligands with the target protein. The visualization results revealed the interactions between amino acid residues and the ligands. The presence of specific amino acid interactions indicates the formation of contact between the ligands and the receptor, thereby suggesting potential inhibitory activity. The binding site area highlighted key amino acid residues that play essential roles in forming interactions such as hydrogen bonds, hydrophobic interactions, and electrostatic interactions (Stamineus et al., 2024). According to the amino acid contact results (Table 3), ligands such as Beta-sitosterol, Fisetin 4'-glucoside, Gallocatechin, Glucogallin, Hirsutrin, Isoquercetin, Lintetralin, Naringenin, and Rutin exhibited strong interactions with angiotensin-converting enzyme (ACE), as evidenced by the number and identity of interacting residues matching those in the target binding site. This suggests that the active/binding pocket of the enzyme where these ligands bind is similar to that of the native ligand, potentially resulting in comparable binding affinities and inhibitory effects on ACE. In contrast, ligands such as Eriodictyol, Kaempferol 4'-rhamnoside, Luteolin 7-O-(2-apiosyl-6-malonyl)- glucoside, and Quercetin did not exhibit strong interactions with ACE, as their interacting residues did not correspond with the key target residues, indicating weaker or non-optimal binding within the active site.

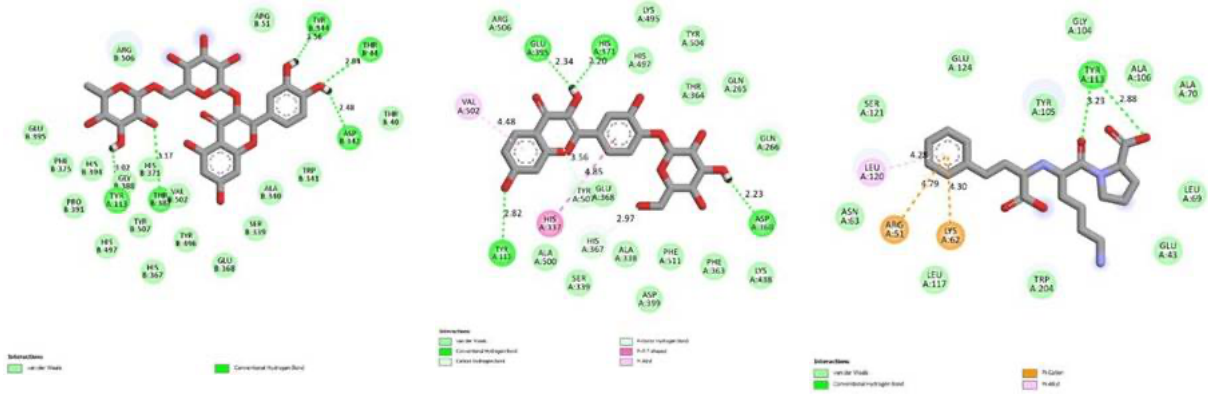

Figure 3. Interaction Visualization of (a) Native Ligand Lisinopril, (b) Fisetin 4'-glucoside, and (c) Rutin

CONCLUSION

This study successfully identified several active compounds from Phyllanthus niruri with strong potential as ACE inhibitor candidates based on an in silico approach using Lipinski's Rule of Five and molecular docking analysis. Of the 32 evaluated compounds, 16 met all Lipinski parameters, indicating pharmaceutical feasibility as oral drugs. Docking analysis revealed that 12 compounds exhibited higher binding affinity than lisinopril, with the best binding energies shown by rutin (-12.0 kcal/mol) and fisetin 4'-glucoside (-11.9 kcal/mol). Molecular interaction visualization demonstrated that these high-affinity compounds interacted with key active residues of the ACE enzyme, which are also the primary interaction sites of lisinopril as the reference ligand. Docking validation with an RMSD value of 0.1207 Å confirmed the reliability of the method used. Overall, the findings of this study reinforce the potential of several Phyllanthus niruri compounds as promising natural ACE inhibitors, with opportunities for further development as plant-based antihypertensive agents.

RECOMMENDATIONS

Based on the findings of this study, it is recommended that the active compounds from Phyllanthus niruri exhibiting high affinity toward the ACE receptor—particularly rutin and fisetin 4′- glucoside—be prioritized for further investigation through in vitro and in vivo biological assays to confirm their actual antihypertensive activity. Toxicity and bioavailability tests are also essential to ensure the safety and efficacy of these compounds as potential oral drug candidates. This study also opens opportunities for the development of phytopharmaceutical formulations based on natural products as a safer and more affordable alternative therapy for hypertension.

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