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In Silico Study of Bay Leaf (Syzygium polyanthum) Compounds as Renin Inhibitors and Antihypertensive Herbal Tea Development

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ABSTRACT

Background : Hypertension is a major global health problem contributing significantly to cardiovascular morbidity and mortality. One of the key pathways in blood pressure regulation is the Renin–Angiotensin–Aldosterone System (RAAS), where renin plays a crucial role as the initiating enzyme. Inhibition of renin is considered a more specific therapeutic strategy with potentially fewer side effects. Bay leaf (Syzygium polyanthum) has been traditionally used as an antihypertensive agent and contains various bioactive compounds **Methods :** This study aims to evaluate the potential of bay leaf compounds as renin inhibitors using an in silico approach and to explore their development into herbal tea products. Active compounds were identified through literature-based LC-MS data, including gallic acid, malic acid, luteic acid, and myricetin. Molecular docking was performed using AutoDock Vina against human renin (PDB ID: 3D91). **Results:** The results showed that myricetin exhibited the highest binding affinity (-9.3 kcal/mol), followed by luteic acid (-7.9 kcal/mol), gallic acid (-6.1 kcal/mol), and malic acid (- 5.1 kcal/mol), compared to the standard inhibitor remikiren (-10.3 kcal/mol). **Conclusions:** Interaction analysis revealed that myricetin formed multiple hydrogen bonds with catalytic residues. These findings suggest that bay leaf compounds, especially myricetin, have potential as natural renin inhibitors and could be developed as antihypertensive herbal tea.

Keyword: Bay leaf; In silico; Renin inhibitor; Molecular docking; Antihypertensive; Herbal tea.

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INTRODUCTION:

Hypertension is one of the leading causes of morbidity and mortality worldwide, contributing significantly to the global burden of cardiovascular diseases such as stroke, chronic kidney disease, and coronary heart disease. It is estimated that more than 1.2 billion people suffer from hypertension globally, making it a major public health concern (Mills et al., 2020). The World Health Organization has identified hypertension as a major risk factor responsible for millions of deaths annually (World Health Organization. (2021). The condition is often referred to as a "silent killer" because it may remain asymptomatic for long periods while progressively damaging vital organs. Persistent

elevation of blood pressure increases the workload of the heart and blood vessels, eventually leading to structural and functional abnormalities (Sliwa & Kahan, 2020).

The pathophysiology of hypertension is complex and involves multiple regulatory systems, among which the Renin–Angiotensin–Aldosterone System (RAAS) plays a central role. This system regulates blood pressure, fluid balance, and electrolyte homeostasis through a cascade of enzymatic reactions and hormonal signaling. Dysregulation of the RAAS contributes significantly to the development and progression of hypertension, making it a primary target for pharmacological intervention (Carey & Siragy, 2003).

Renin, an aspartyl protease enzyme secreted by the juxtaglomerular cells of the kidney, serves as the initial and rate-limiting enzyme in the RAAS cascade. It catalyzes the conversion of angiotensinogen into angiotensin I, which is subsequently converted into angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor that increases blood pressure by promoting vascular resistance, sodium retention, and aldosterone secretion. Consequently, inhibition of renin can effectively suppress the entire RAAS pathway at its earliest stage (Fountain & Lappin, 2023).

Given its upstream role in the RAAS cascade, renin has emerged as an attractive therapeutic target for hypertension management. Inhibiting renin offers several advantages compared to targeting downstream components, as it may provide more comprehensive suppression of the

system and reduce compensatory mechanisms. This approach is expected to improve the effectiveness of antihypertensive therapy (Carey & Siragy, 2003).

Synthetic renin inhibitors, such as remikiren, have demonstrated strong inhibitory activity and effectiveness in reducing blood pressure. However, their clinical use is often associated with limitations, including high cost, limited availability, and potential side effects. These challenges highlight the need for alternative therapeutic agents that are more accessible, cost- effective, and safer for long-term use (Matsuno et al., 2018).

In recent years, natural products have gained considerable attention as potential sources of antihypertensive agents. Plant-derived compounds are known for their structural diversity and wide range of biological activities, including antioxidant and cardioprotective effects. Many natural compounds exhibit pharmacological activity with relatively low toxicity, making them attractive candidates for drug development (Scalbert et al., 2005).

Bay leaf (Syzygium polyanthum), widely used in traditional medicine in Southeast Asia, has been reported to possess various pharmacological properties, including antihypertensive, antioxidant, and anti-inflammatory activities. The plant contains a wide range of bioactive compounds such as flavonoids, phenolic acids, and tannins, which contribute to its therapeutic potential. However, the molecular mechanisms underlying its antihypertensive activity, particularly its interaction with the renin enzyme, remain limited (Sabandar et al., 2022).

Flavonoids and phenolic compounds have been extensively studied for their role in cardiovascular protection. These compounds are known to modulate oxidative stress, improve endothelial function, and inhibit enzymes involved in blood pressure regulation. Additionally, their polyphenolic structures enable interactions with target proteins, supporting their role as potential enzyme inhibitors (Scalbert et al., 2005).

In this context, in silico approaches, particularly molecular docking, have become valuable tools in modern drug discovery. Molecular docking allows the prediction of ligand–protein interactions, binding affinity, and binding modes efficiently and cost-effectively. This method enables rapid screening of multiple compounds and serves as an important preliminary step before experimental validation (Trott & Olson, 2010). Despite the growing interest in natural antihypertensive agents, previous studies have predominantly focused on the inhibitory effects of plant-derived compounds on angiotensin-converting enzyme (ACE) rather than targeting renin as the upstream regulator in

the Renin–Angiotensin–Aldosterone System (RAAS). Several studies have reported the antihypertensive potential of flavonoids and phenolic compounds through ACE inhibition and antioxidant mechanisms (Perez-Vizcaino & Duarte, 2010; Scalbert et al., 2005). In addition, molecular docking studies have identified various plant-derived compounds, such as quercetin and catechin, as potential inhibitors of RAAS-related enzymes, primarily ACE rather than renin (Meng et al., 2011). Furthermore, although Syzygium polyanthum has been widely reported for its antihypertensive activity in traditional medicine and supported by phytochemical and pharmacological studies (Sabandar et al., 2022), its specific mechanism of action at the molecular level—particularly its interaction with renin—remains poorly explored. Most existing studies emphasize its antioxidant, anti-inflammatory, or general cardiovascular effects without elucidating its role as a direct renin inhibitor. In comparison, synthetic renin inhibitors such as remikiren and aliskiren have been extensively studied and demonstrate strong binding affinity and clinical efficacy (Wood et al., 2003; Matsuno et al., 2018). However, studies investigating natural compounds with comparable activity toward renin are still limited, especially those integrating computational approaches with potential functional food development. Therefore, a clear research gap exists in: the limited exploration of renin inhibition by plant-derived compounds compared to ACE inhibition, the lack of molecular-level evidence regarding the interaction of Syzygium polyanthum compounds with renin, and the absence of studies linking in silico findings with practical applications such as herbal tea development. This study addresses these gaps by evaluating the renin inhibitory activity of bay leaf compounds using molecular docking and exploring their potential application as an antihypertensive herbal tea.

Therefore, this study aims to evaluate the inhibitory activity of bioactive compounds from bay leaf (Syzygium polyanthum) against the renin enzyme using molecular docking analysis. Additionally, this research seeks to explore the potential application of bay leaf as a functional food in the form of herbal tea for hypertension management. By integrating computational analysis with traditional knowledge, this study is expected to provide scientific evidence supporting the development of natural antihypertensive therapies.

METHODS:

Research Design

This study employed an in silico exploratory approach using molecular docking to evaluate the inhibitory potential of bioactive compounds from Syzygium polyanthum against the renin enzyme. The molecular docking study was performed using AutoDock Vina to evaluate the interaction between selected compounds and the renin enzyme. The three-dimensional structure of renin was obtained from the Protein Data Bank and prepared by removing water molecules, deleting the native ligand, adding polar hydrogen atoms, and assigning Kollman charges. Ligands were prepared by energy minimization using the MMFF94 force field, followed by the addition of hydrogen atoms and assignment of Gasteiger charges, and saved in .pdbqt format. The grid box was centered on the active site based on the native ligand position, with a grid size of 25 × 25 × 25 Å. Docking was carried out with an exhaustiveness value of 8–16, generating up to 9 binding poses for each ligand. Method validation was performed by redocking the native ligand, and a root mean square deviation (RMSD) value ≤ 2.0 Å was considered acceptable. The docking results were analyzed based on binding affinity (kcal/mol) and molecular interactions, including hydrogen bonding and hydrophobic interactions, particularly with key active site residues (Asp32 and Asp215).

Materials Ligands

The compounds analyzed included gallic acid, malic acid, luteic acid, and myricetin. Remikiren was used as a positive control, and the native ligand (REM350) was used for validation.

Protein Target

The three-dimensional structure of human renin (PDB ID: 3D91) was obtained from the Protein Data Bank.

Software

PyMOL, AutoDock Tools, AutoDock Vina, Discovery Studio Visualizer, and Open Babel.

Methods

Ligand Preparation

Ligand structures were obtained from PubChem, converted into PDB format, and energy minimized. Polar hydrogens and Gasteiger charges were added before conversion to PDBQT format.

Protein Preparation

The protein was prepared by removing water molecules and native ligands. Hydrogen atoms and charges were added, followed by conversion to PDBQT format.

Docking Validation

Validation was performed by redocking the native ligand. The RMSD value obtained was 0.433 Å, indicating acceptable accuracy (≤2.0 Å).

Molecular Docking

Docking was performed using AutoDock Vina. Binding affinity values (kcal/mol) were recorded.

Data Analysis

a. Binding affinity evaluation
b. Molecular interaction analysis
c. Comparative analysis with standard inhibitor

RESULTS:

Identification of Bioactive Compounds

Based on Liquid Chromatography–Mass Spectrometry (LC–MS) literature data, bay leaf (Syzygium polyanthum) contains several major bioactive compounds, including gallic acid, malic acid, luteic acid, and myricetin, which belong to phenolic and flavonoid groups. These compounds are known to exhibit various biological activities, particularly antioxidant and potential antihypertensive effects due to their ability to interact with target proteins (Rice- Evans et al., 1996; Perez-Vizcaino & Duarte, 2010).

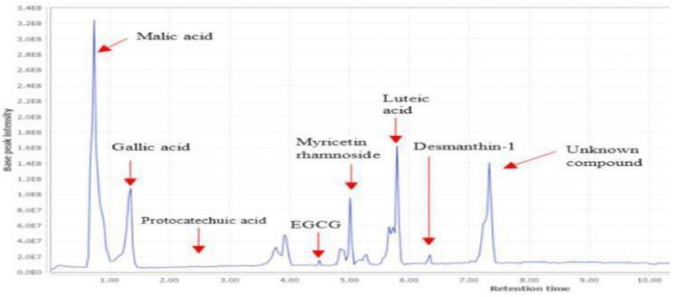
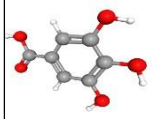
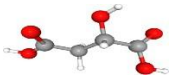
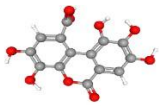
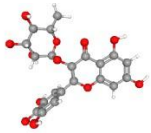
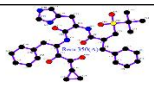


Figure 1. Total Ion Cromatogram of Syzygium polyanthum

Ligan Preparation

The preparation of ligands involved obtaining the three-dimensional (3D) structures of the identified compounds from Syzygium polyanthum. The compounds analyzed in this study included gallic acid, malic acid, luteic acid, and myricetin derivatives. In addition, the native ligand (REM350) and the standard inhibitor remikiren were used as references to validate docking results and compare binding affinities.

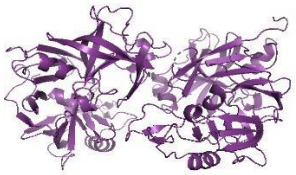
Table 1. structure of test ligands from of Syzygium polyanthum

No	Compound	Structure 3 D
1	Asam Galat	
2	Asam malat	
3	Luteic Acid	
4	Myricetin 3-O-alpha- L-rhamnopyranoside	
5	Native Ligan (REM 350 (A)	
6	Kontrol posistif / Remikiren	

Protein Preparation

The receptor used in this study was renin enzyme with PDB ID 3D91, which contains the native ligand REM350. Protein preparation involved removing water molecules, adding hydrogen atoms, and optimizing the structure prior to docking analysis to ensure accurate ligand–protein interaction prediction (Trott & Olson, 2010).

Table 2. List of Native Ligan For Receptor

Reseptor	Structure	Native Ligand
3D91		REM350

Validation Of Docking

Docking validation was performed using the re-docking method of the native ligand into the receptor binding site. The Root Mean Square Deviation (RMSD) value obtained was **0.433 Å**, indicating that the docking protocol used in this study is valid and reliable, as RMSD values below 2.0 Å are generally considered acceptable for docking validation (Trott & Olson, 2010).

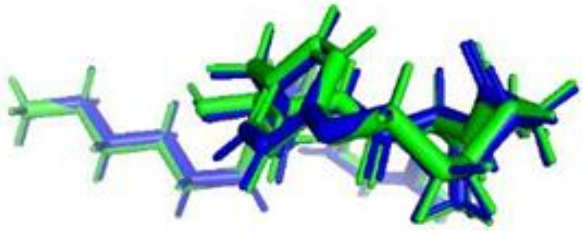


Figure 2. Conformation of Native Ligand Structure with re-docking results

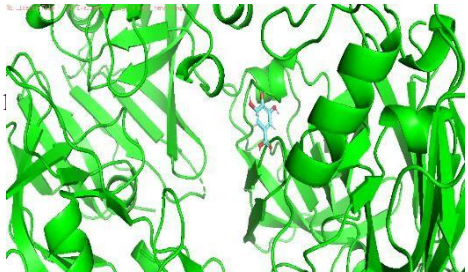
The RMSD value obtained was **0.433 Å**, indicating that the docking method is valid and reliable.

Binding Affinity Results

The molecular docking results demonstrated that all tested compounds were able to bind to the active site of the renin enzyme with varying binding affinities. Remikiren, as the standard inhibitor, exhibited the strongest binding affinity of –10.3 kcal/mol, followed by myricetin with –9.3 kcal/mol, which was relatively close to the standard inhibitor. This suggests that myricetin has strong potential as a renin inhibitor.

Table 3. Redocking results

Ligand	Binding Affinity (kcal/mol)



Remikiren	-10.3
Myricetin	-9.3
Native Ligand	-8.5
Luteic Acid	-7.9
Gallic Acid	-6.1
Malic Acid	-5.1

The differences in binding affinity may be influenced by the structural complexity and functional groups of each compound, which determine the strength and type of interactions formed within the active site (Meng et al., 2011).

Molecular Interaction Analysis

The analysis of molecular interactions revealed variations in the number of interactions between ligands and the renin enzyme. Luteic acid, native ligand, and remikiren showed the highest number of interactions (6 interactions), followed by myricetin (5 interactions), gallic acid (2 interactions), and malic acid (1 interaction).

Table 4. Interaction Analysis

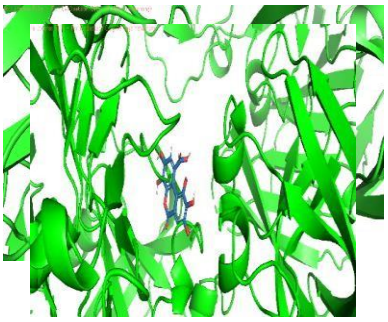
Compound	Number of Interactions
Malic Acid	1
Gallic Acid	2
Myricetin	5
Luteic Acid	6
Native Ligand	6
Remikiren	6

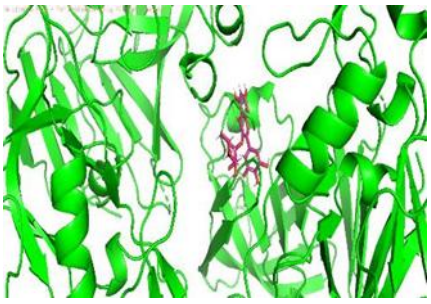
These interactions include hydrogen bonding, hydrophobic interactions, and electrostatic interactions, which collectively contribute to the stability of ligand–protein complexes (Meng et al., 2011).

Visualization

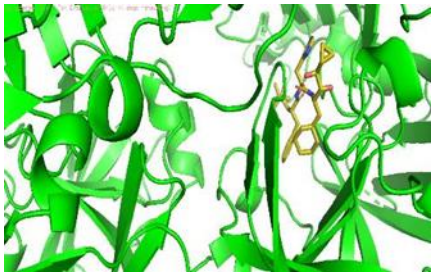
Visualization of docking results was performed to observe the binding orientation and interaction sites of each ligand within the active site of renin. The results showed that all compounds occupied the binding pocket, although with different conformations and interaction patterns.

Gallic Acid
Malic acid

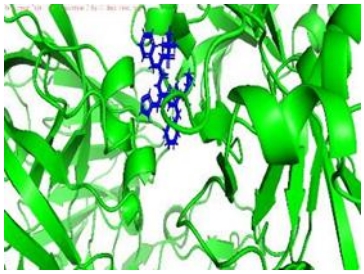




Myricetin Rhamnoside

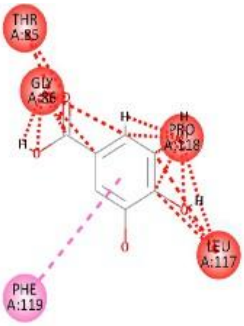


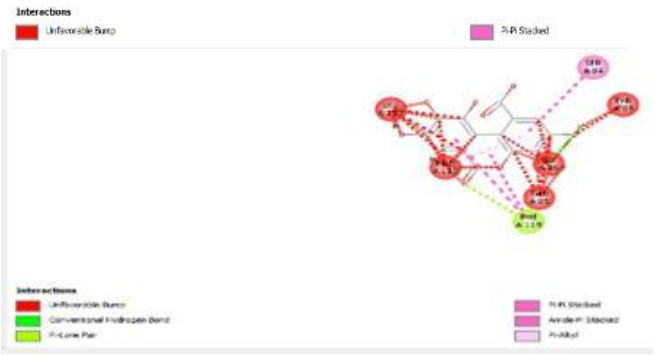
Native Ligan REM 350 (A)



Remikiren

Figure 3. Visualization between Receptor and Ligand





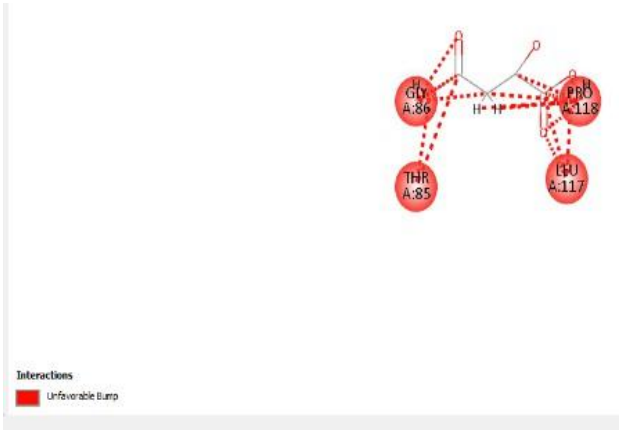
Luteic Acid has 6 interaction

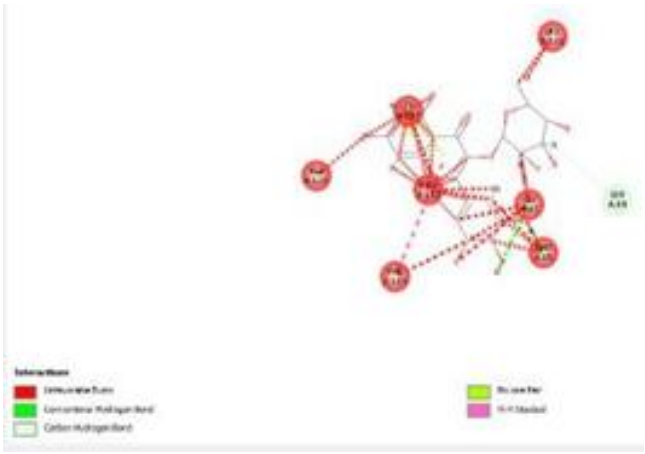
Interaction

Further interaction mapping demonstrated that each compound formed specific interactions with amino acid residues in the active site. Malic acid exhibited only one interaction, while gallic acid formed two interactions. Myricetin formed five interactions, indicating a relatively stable binding. Luteic acid, native ligand, and remikiren showed the highest number of interactions (six interactions), suggesting strong binding stability.

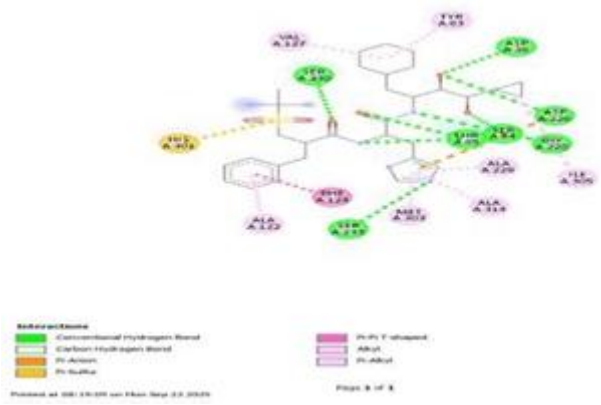
Malic Acid has 1 interaction

Gallic acid has 1 interaction

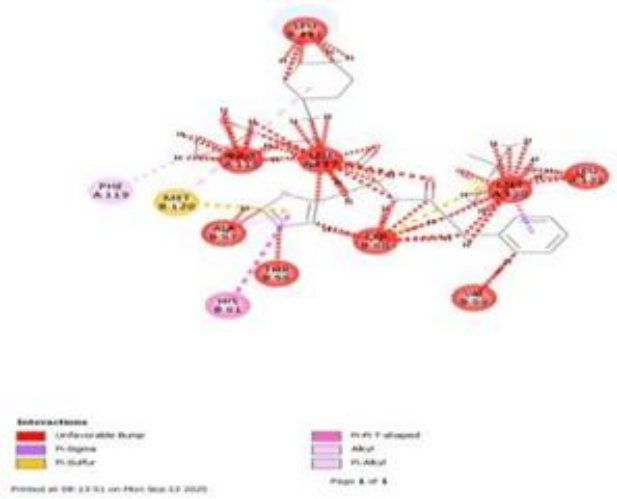




Myricetin has 5 interaction



Native Ligan has 6 interaction



Remikiren has 6 interaction

Figurre 4. Interaction between receptors and ligands

DISCUSSION:

Knowledge is the result of human This study provides a comprehensive in silico evaluation of the renin inhibitory potential of bioactive compounds derived from bay leaf (Syzygium polyanthum), highlighting their relevance as alternative antihypertensive agents. Renin plays a pivotal role in the Renin–Angiotensin–Aldosterone System (RAAS), acting as the rate-limiting enzyme that initiates the cascade leading to the formation of angiotensin II, a potent vasoconstrictor. Therefore, inhibition of renin represents a rational and targeted approach to controlling blood pressure at its earliest stage (Atlas, 2007; Fyhrquist & Saijonmaa, 2008). The identification of natural renin inhibitors is particularly important due to the limitations associated with synthetic drugs, including cost, accessibility, and potential adverse effects (Stanton, 2003). Several previous studies have primarily focused on ACE inhibition rather than renin targeting. For instance, flavonoid-rich extracts such as Orthosiphon stamineus demonstrated significant ACE inhibitory activity supported by molecular docking, where flavonoids interact with the zinc-binding active site of ACE (Shafaei et al, 2016) . Similarly, quercetin glycosides showed strong binding affinity (−8.5 kcal/mol), even comparable to standard ACE inhibitors, indicating their potential as antihypertensive agents (Syed Aun Muhammad and Nighat Fatima, 2015) . Structure–activity relationship studies also confirmed that various flavonoids (e.g., luteolin, quercetin) exhibit notable ACE inhibition, with IC_{50} values ranging from 23–196 μM (Guerrero et al, 2012).

The molecular docking results demonstrated that all tested compounds exhibited binding affinity toward the renin active site, indicating their potential as inhibitory agents. Among them, myricetin showed the most favorable binding affinity (-9.3 kcal/mol), which was comparable to that of the standard inhibitor remikiren (-10.3 kcal/mol). This finding suggests that myricetin possesses strong binding capability and may effectively compete with endogenous substrates or inhibitors for occupancy of the active site (Wood et al., 2003). The relatively small difference in binding affinity between myricetin and remikiren further supports its potential as a natural alternative for renin inhibition.

The superior binding affinity of myricetin can be attributed to its structural characteristics, particularly its polyphenolic framework enriched with multiple hydroxyl groups. These functional groups facilitate the formation of hydrogen bonds with key amino acid residues within the renin active site. Notably, interactions with catalytic residues such as Asp32 and Asp215 are essential for inhibitory activity, as these residues are directly involved in the catalytic mechanism of renin (Atlas, 2007; Rahuel et al., 2000). The ability of myricetin to engage these residues suggests a mechanism of action that may involve blocking substrate access or disrupting enzymatic catalysis.

In addition to hydrogen bonding, other non-covalent interactions, including hydrophobic interactions and π–π stacking, are likely to contribute to the stability of the myricetin–renin complex. The presence of aromatic rings in myricetin enables interactions with hydrophobic regions within the binding pocket, enhancing binding affinity and overall complex stability. Such multi-modal interactions are critical in determining the strength and specificity of ligand–protein binding (Meng et al., 2011),

further reinforcing the potential of myricetin as a lead compound.

Luteic acid exhibited moderate binding affinity (-7.9 kcal/mol) and formed multiple interactions with the active site residues, indicating a relatively stable binding configuration. Interestingly, luteic acid demonstrated a higher number of interactions compared to myricetin, suggesting that it can effectively occupy the binding pocket. However, despite the higher interaction count, its binding affinity was lower, indicating that not all interactions contribute equally to binding strength. This highlights the importance of interaction quality, orientation, and involvement of key residues rather than merely the number of interactions (Meng et al., 2011).

In contrast, gallic acid and malic acid showed weaker binding affinities (-6.1 kcal/mol and - 5.1 kcal/mol, respectively), which may be explained by their simpler molecular structures. These compounds possess fewer functional groups and limited structural complexity, resulting in reduced opportunities for forming strong and specific interactions with the active site. Consequently, their inhibitory potential is likely lower compared to more structurally complex compounds such as myricetin (Rice-Evans et al., 1996).

A critical observation in this study is that binding affinity is not solely determined by the number of interactions but also by the type and strength of those interactions. Strong hydrogen bonds with catalytic residues, hydrophobic interactions within the binding pocket, and proper ligand orientation significantly influence binding stability (Meng et al., 2011). This is evident in the case of myricetin, which, despite having fewer interactions than luteic acid, demonstrated stronger binding affinity due to more favorable interaction characteristics.

When compared with the native ligand and the standard inhibitor remikiren, myricetin demonstrated competitive binding behavior, suggesting that it may effectively inhibit renin activity. The docking validation result, indicated by a low RMSD value (0.433 Å), confirms the reliability of the docking protocol used in this study (Trott & Olson, 2010). This strengthens the credibility of the predicted binding interactions and supports the potential of myricetin as a promising candidate for further investigation.

These findings are consistent with previous studies that have identified flavonoids as potential antihypertensive agents. Flavonoids are known to exhibit multiple biological

activities, including antioxidant effects and enzyme inhibition within the RAAS pathway. The ability of flavonoids to modulate key enzymes involved in blood pressure regulation further supports their potential role in cardiovascular disease management (Perez-Vizcaino & Duarte, 2010). Therefore, the presence of myricetin in bay leaf reinforces its potential as a natural source of antihypertensive compounds.

From an application perspective, the identification of renin-inhibiting compounds in bay leaf supports its development as a functional food or herbal tea for hypertension management. Herbal-based interventions offer several advantages, including lower toxicity, better patient compliance, and wider accessibility, particularly in regions where traditional medicine is widely practiced (Ekor, 2014). The formulation of bay leaf into herbal tea represents a practical and culturally acceptable approach to delivering these bioactive compounds.

Despite these promising findings, this study has several limitations. The use of in silico methods provides predictive insights into molecular interactions but does not fully capture the complexity of biological systems. Factors such as bioavailability, metabolism, pharmacokinetics, and toxicity cannot be accurately assessed through docking studies alone (Trott & Olson, 2010). Therefore, further validation through in vitro and in vivo studies is essential to confirm the biological activity, safety, and therapeutic efficacy of these compounds.

Future research should focus on experimental validation of the renin inhibitory activity of myricetin and other compounds, as well as the development of optimized formulations for clinical use. Additionally, studies exploring synergistic effects between compounds may provide further insights into the therapeutic potential of bay leaf. Such

investigations will be crucial in translating these findings into practical applications for hypertension management..

CONCLUSIONS:

This study demonstrates that bioactive compounds from bay leaf (Syzygium polyanthum), particularly myricetin, have significant potential as natural renin inhibitors based on molecular docking analysis. Myricetin exhibited strong binding affinity and stable interactions with the renin active site, approaching the activity of the standard inhibitor remikiren. These findings suggest that bay leaf could be developed as an antihypertensive herbal tea. Further experimental studies are necessary to validate these results and support clinical applications.

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