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RESEARCH ARTICLE OPEN ACCESS

MOLECULAR DOCKING ANALYSIS OF ACTIVE COMPOUNDS OF STAR FRUIT PLANTS WULUH (Averrhoa bilimbi. L) AGAINST NEPRILYSIN RECEPTORS AS ANTIHYPERTENSIVE DRUG CANDIDATES

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ABSTRACT
Hypertension is a major global health problem that significantly increases the risk of cardiovascular diseases. Neprilysin plays an essential role in blood pressure regulation and has emerged as a promising therapeutic target for antihypertensive drug development. This study aimed to evaluate the potential of active compounds from Averrhoa bilimbi L. as neprilysin inhibitors using an in silico approach. Molecular docking was performed between selected phytochemical compounds (Isocytisoside, Hallacton B, Vitexin 4″-O-rhamnoside, Epiafzelechin 3-O-gallate, and 2,4,6-Triphenyl-1-hexene) and the neprilysin receptor (PDB ID: 5JMY) using AutoDockTools. Docking protocol validation was conducted by redocking the native ligand, with validity determined by an RMSD value ≤ 3 Å. The grid box was set at coordinates x = −20.579, y = 3.317, z = 37.541 with dimensions of 40 × 40 × 40. Physicochemical properties and ADMET profiles were predicted using the pkCSM online server. The docking validation yielded an RMSD value of 1.303 Å, confirming the reliability of the docking protocol. Among the tested compounds, Hallacton B exhibited the most favorable binding affinity among the test ligands, with a binding energy of −9.45 kcal/mol and an inhibition constant (Ki) of 117.49 µM, along with key amino acid interactions comparable to the reference drug sacubitril. ADMET analysis indicated that Hallacton B possesses a favorable safety profile, showing negative results for Ames toxicity and hepatotoxicity, no inhibition of CYP2D6 and CYP3A4 enzymes, and acceptable distribution characteristics, although its intestinal absorption was relatively low (16.71%). Hallacton B demonstrates promising potential as a natural neprilysin inhibitor and warrants further optimization and experimental validation through in vitro and in vivo studies.

Keywords: hypertension, Averrhoa bilimbi, neprilysin, molecular docking, ADMET

INTRODUCTION
Hypertension is often referred to as a silent killer because it often does not show symptoms. Many people with hypertension feel healthy despite their high blood pressure (Gustam et al., 2024). Hypertension or high blood pressure in Indonesia is a health problem that has received attention of the public health service system. This condition is the main risk factor for various chronic diseases such as heart, stroke, kidney failure, and other health problems that can significantly lowering the individual's quality of life. Based on data from the Ministry of Health of the Republic of Indonesia, The prevalence of hypertension continues to increase from year to year, which has a wide impact on both to public health and the country's economic burden. (Rokom, 2023).

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Based on data on Health Services for Hypertension Patients by Gender, District, and Health Center in Jember Regency in 2024, the estimated number of hypertensive patients aged ≥15 years in Jember Regency is 163,865 people, consisting of 81,109 men and 82,756 women. Of these, 148,085 people or 90.4% received health services with hypertension, with details of 61,292 men (75.6%) and 86,793 women (104.9%). The services of hypertension patients are spread throughout sub-districts and health centers in Jember Regency, showing that the coverage of hypertension health services in general is high, especially in the female group, although in some areas there is still a variation in the percentage of service achievement between men and women.

Treatment of hypertension generally involves the use of antihypertensive drugs, one of which is a combination of sacubitril/valsartan. Nevertheless, the use of sacubitrile has some limitations. Sacubitril is more likely to cause symptomatic hypotension with systolic blood pressure <90 mmHg than enalapril, so special caution is required especially in patients with low blood pressure. In addition, the risk of side effects such as hypotension, hyperkalemia, impaired renal function, angioedema, and cough may lead to a decrease in the dose of therapy which is known to be associated with an increased risk of primary outcomes. In some subgroups of patients, such as patients with a history of heart failure hospitalization in the previous 3–6 months, certain age groups, and certain clinical score categories, sacubitril/valsartan did not show a significant benefit over enalapril on primary outcomes or mortality. The effectiveness of sacubitril/valsartan was also reported to be lower in patients with low systolic blood pressure compared to patients with higher systolic blood pressure.

As an alternative therapy, the use of natural ingredients such as star fruit (Averrhoa bilimbi L.) continues to be developed because the fruit is reported to be more effective in lowering blood pressure than the leaves. Starfruit contains flavonoids, potassium, and vitamin C which play a role in antihypertensive mechanisms. Flavonoids are able to increase endothelial relaxation through the activation of endothelial nitric oxide synthase (eNOS) thereby increasing the production of nitric oxide (NO) and prostasicline which are vasodilators. Potassium content plays a role in inhibiting renin secretion, reducing the formation of angiotensin II, inhibiting sodium reabsorption

and water in the kidneys, as well as triggering dilatation of blood vessels thereby reducing peripheral resistance and intravascular fluid volume. Meanwhile, vitamin C functions as an antioxidant that lowers oxidative stress and increases the bioavailability of NO, thereby improving endothelial function and supporting blood pressure reduction (Ahmad Yani et al., 2022).

To study the potential of these active compounds more efficiently, the in silico approach is used as an initial stage in the discovery of antihypertensive drugs. This method allows analysis of the interaction of compounds with target receptors, evaluation of physicochemical properties based on Lipinski's Rule of Five, as well as assessment of pharmacokinetic and safety profiles through ADMET parameters. Nevertheless, in silico prediction results still require further validation through in vitro and in vivo tests. Therefore, this study aims to evaluate the potential of active compounds from star fruit as an antihypertensive drug candidate using an in silico approach.

MATERIAL AND METHODS

Tools

The Hardware used is a set of ASUS computers with Intel Core i3-1045H specifications with Windows 11 64 bit operating system, MarvinSketch version 24.1.0,

AutodockTools version 1.5.6., PyRx version 0.9.8, Molegro Molecul Viewer version 2012.2.5, BIOVIA Discovery Studio version 24.1.0, and other online server-based helper programs such as Lipinski Rule of five

Ingredients

The material used in this study is Protein in Silico which is widely used in drug discovery and development because it is able to predict molecular interactions efficiently and economically (Pinzi & Rasteli, 2019). The test ligand used in this study is a compound test ligand from the Star Star Wuluh plant (Averrhoa bilimbi. L) namely Isocytisoside, Hallacton B, Vitexin 4"-o-rhamnoside, Epiafzelechin 3-O-gallate, d2,4,6 Triphenyl-1-hexene and also used Neprilysis receptors with PDB ID 5JMY with Sacubtril comparator ligands.

Prediksi Sifat Kimia (Lipinski's Rule of Five)

Prediction of physicochemical properties was carried out using the pkCSM online tool. First, all the compounds used are drawn in a 2-D molecular structure and then copied in the Chem3D Pro 12.0 program to create a 3-D structure, which is then stored in the form of a *.sdf file. then the structure is translated into a form of SMILES format using the help of Online SMILES Translator (https://cactus.nci.nih.gov/translate/). In the form of SMILES format, the compounds were then processed using pkCSMonlinetool (https://biosig.lab.uq.edu.au/pkcsm/) to predict ADME and toxicity of compounds (Dwi Khrihariyani.et al., 2020).

Ligan Preparation

The molecular structure of 2D Ligands is obtained from the PubChem Web Browser (https://pubchem.ncbi.nlm.nih.gov/) database. It is then prepared and computed using MarvinSketch software version 24.1.0 With MarvinSketch software version 24.1.0, the results of protonation and conformation are obtained by looking for the lowest ligand bond energy values. Then the files in this final structure are stored in two different file formats, namely PDB and mol2 using BIOVIA Discovery Studio version 24.1.0.

Protein Preparation

Download 3D structure in RCSB Protein Data Bank with PDB code 5JMY. Next is done preparation of target proteins before the docking process, i.e. by removing water molecules and ligands Disruptors that are not docked using Molegro Molecular Viewer software version 2012.2.5, Then the result is saved in (.pdb) format. Then add hydrogen atoms to the natural ligands and protein using BIOVIA Discovery Studio software version 24.1.0.

Docking Validation

The molecular docking method validation process is carried out by redocking between native ligands that have been separated from the target protein by the AutodockTools1.5.6 program. The validity of this method is declared valid with the RMSD (root mean square distance) value parameter. The docking method is considered valid if the RMSD value ≤ 3 Å. The smaller the RMSD value, the more accurate the prediction of the position of the ligand as it approaches its original conformation (Gede Ngurah, 2021). Docking validation is done in 100 runs, and the output of this process is gridbox and RMSD value. The gridbox setting in the docking process is used to determine the ligand-binding space that will be docked.

Analysis of Docking Results Visualization

Molecular docking is done using AutodockTools software version 1.5.6., with the initial stage is in the form of preparation of receptors and ligands obtained from the Protein Data Bank (PDB) web server and stored. The protein and ligand files were further opened and analyzed using BIOVIA Discovery Studio 2016. Then the validation method is carried out by re-docking the original ligand (native ligand) that has previously been separated from the

receptor. The process of visualization or interaction analysis is carried out to be able to see the results of tethering between the comparison ligand and the compound test ligand used. So that after the process of visualization of the test ligand, will be displayed in 2D using the Discovery Studio application version 24.1,0 (Hadi Soebroto et.al., 2025).

RESULT AND DISCUSSION

The preparation of the ligand is an important stage in molecular docking because it affects the conformal stability of the ligand before it interacts with the receptor. This stage includes the addition of hydrogen atoms, partial charge determination, geometry optimization, and energy minimization to achieve conformance with minimum energy. The results of ligand preparation in this study showed a varied energy range, with the lowest energy value of -10.23 and the highest of -5.91. The ligands with the lowest energy exhibit the most thermodynamically stable conformation, thus potentially forming more stable and consistent interactions with the active side of the receptor. In contrast, high-energy ligands reflect less stable conformations, possibly due to steric resistance or suboptimal functional group orientation, making them less suitable for advanced docking analysis. Therefore, low-energy ligands are prioritized in in silico studies to increase the validity of the results of ligand-receptor interactions (Farhah.et al., 2022).

Docking Method Validation

This validation is carried out by re-anchoring the natural ligands to the receptor using the AutoDock application and then adjusting the size and position of the grid box. In this study, the grid box used has the following values, Grid Box (x = 40; y = 40; z = 40), Grid Coordinate (x = -20,579; y = 3,317; z = -37,541). Furthermore, the molecular tethering stage of the test ligand to the receptor or target protein is carried out using the same stage as in the validation stage but using the Lamarckian Genetic Algorithm with a value of 100. In the validation process, the value of the genetic algorithm used is smaller than during the running process for molecular tethering of the test ligand. The goal is that the validation process can be obtained faster with results that are not much different from the results of running using a larger genetic algorithm. According to the literature, the large value of genetic algorithms in such a running process does not show a significant contribution related to the validity of the results of molecular tethering using AutoDock.14. The results of molecular tethering are then analyzed using AutoDock to determine the best bond energy value and KI (Inhibition Constant) of each ligand tested. The results of the analysis were then visualized using the BIOVIA Discovery Studio application version 24.1.0. to obtain 2D and 3D visualization forms of test ligands that have been tethered to the receptor (Farhah, et al. 2022).

The validation of this method is declared valid with the RMSD (root mean square distance) value parameter. The docking method is considered valid if the RMSD value ≤ 3 Å. The smaller the RMSD value, the more accurate the ligand position prediction will be as it approaches its original conformation. The purpose of method validation is to prove and ensure that the method used meets the validity requirements and can be used in testing other compounds so that errors can be minimized. Optimization and determination of the gridbox are carried out with the Autodock application, the determination of the grid box (bonding area) is carried out to determine the ligand mooring space in the molecular tethering process (Gede Ngurah.et al. 2021). The results of the protein docking visualization were obtained from the grid box (Table 1) from running 100 dockings, with the best conformation found in the 70th run with a binding energy value of -10.23 Kcal/mol.

The results of the method validation resulted in an RMSD value of ≤ 3 Å, which is 1,303Å so that the method used in this study was declared valid so that the grid box arrangement, namely the coordinates of the space where the test compound and the bound protein, can be used in the docking process of the test compound with the target protein (Devia.et al., 2026).

The molecular docking study was conducted to evaluate the affinity and interaction patterns of several test compounds with protein targets by comparing them to a positive control ligand, namely sacubitrile (Ligand 1). The main parameters analyzed included binding energy, inhibition constant (Ki), RMSD value, and type and number of amino acid interactions, especially residues that are the same as control ligands.

Sacubitril exhibits the lowest binding energy, at –11.36 kcal/mol, as well as the smallest Ki value (4.71 μM), which indicates the strongest bond affinity to protein targets. The sacubitrile interaction is dominated by 9 hydrophobic bonds without the formation of hydrogen bonds. Important residues involved include PHE689, PHE544, VAL692, VAL580, MET579, ARG102, ARG110, ARG717, and HIS711. The abundance of hydrophobic residues indicates that the active sac of proteins is predominantly hydrophobic and highly compatible with sacubitrile structures, thus making it a valid benchmark standard.

Isocytisoside has a binding energy of –9.19 kcal/mol with a Ki value of 182.28 μM, higher than sacubitril, indicating a weaker affinity. However, these compounds form 5 hydrogen bonds and 5 hydrophobic bonds, with the involvement of important residues such as ARG717, TRP693, and PHE689, which also interact with sacubitril. The presence of hydrogen bonds shows good stability of the complex, although thermodynamically it is still inferior to positive controls.

Hallacton B showed a binding energy of –9.45 kcal/mol and a Ki value of 117.49 μM, better than Isocytisoside. These compounds form 4 hydrogen bonds and 6 hydrophobic bonds, with key residues such as PHE544, VAL580, MET579, TRP693, and HIS711 also found in sacubitrile interactions. The balanced combination of hydrogen and hydrophobic bonds shows the potential for good stability of the complex.

Vitexin 4"-O-rhamnoside has a bond energy of –8.84 kcal/mol with a Ki value of 330.69 μM, which is the weakest affinity among the test compounds. Although it forms 5 hydrogen bonds and 5 hydrophobic bonds, the relatively high bond energy indicates a less than optimal interaction with the active side of the protein, so its potential as an inhibitor is lower. Epiafzelechin 3-O-gallate exhibits a bond energy of –9.42 kcal/mol and Ki of 123.79 μM, close to Hallacton B. The compound forms 6 hydrogen bonds and 4 hydrophobic bonds, with the involvement of important residues such as ARG102, ARG717, MET579, VAL580, and HIS711, which It is also a key residue in sacubitril. The most abundant amount of hydrogen bonds among the test compounds indicates good interaction stability on the active side of the protein.

2,4,6-Triphenyl-1-hexene has a bond energy of –9.01 kcal/mol and a Ki of 250.57 μM, with 7 hydrophobic bonds without hydrogen bonds. This pattern resembles sacubitrile which is also dominated by hydrophobic interactions, but the higher bond energy and Ki values indicate a lower affinity than positive controls.

Overall, Hallacton B can be established as the best ligand among test compounds due to its combination of the most stable bond energy, relatively low Ki values, and similarity of interaction residues with sacubitril. Epiafzelechin 3-O-gallate is in second place and has the potential to be a promising alternative inhibitor candidate. These results support the potential of the two compounds to be further investigated through in vitro and in vivo studies to confirm their biological activity.

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Test Results Lipinski's Rule of Five

DrugScan or Lipinski's rule of five prediction screening which refers to the oral administration of drugs has to do with the process of absorption and distribution of drugs and for good parameters or criteria must be based on Lipinski's rules. The application data can be seen in table 3, the results obtained from the test that some compounds do not meet all the criteria of Lipinski's Rule of Five rule that are used to be drug candidates and have the potential to be administered orally.

Based on Lipinski's Rule of Five, physicochemical parameters are used to predict the potential oral bioavailability of a compound. Table 3 shows that Sacubitril and Hallacton B have molecular weights below 500 g/mol and the number of hydrogen bond donors and acceptors that still meet the Lipinski criteria, so they have the potential to have good oral absorption, although the molar refractivity values are relatively high. Meanwhile, Isocytoside shows a tendency to violate Lipinski's rule on the number of donors and hydrogen bond acceptors, which can decrease membrane permeability. Furthermore, Vitexin 4'-O-rhamnoside exhibited the most significant violation of the Lipinski rule, judging from the molecular weight exceeding 500 g/mol and the high number of donors and hydrogen bond acceptors, so it is estimated to have low oral bioavailability. In addition, Epigallocatechin 3-O-gallate and 2,4,6-Triphenyl-1-hexene exhibit very high log P values, indicating an extreme lipophilic property that has the potential to inhibit solubility and systemic distribution. Overall, these predictive results suggest that not all compounds meet Lipinski's criteria, potentially affecting its eligibility as an oral drug candidate.

In silico evaluation of ADMET using pkCSM provides a preliminary picture of feasibility pharmacokinetics and safety of test compounds compared to positive controls of sacubitril. Absorption parameters shows a clear difference between the compounds. Sacubitril has moderate intestinal absorption (62.679%) and the permeability of Caco-2 is very high, reflecting good oral bioavailability. In contrast, Hallacton B, Isocytisoside, and Vitexin 4"-O-rhamnoside show low to moderate absorption, which can be attributed to with large molecular size and high polarity, as commonly reported in flavonoid compounds and glycosides. Epiafzelechin 3-O-gallate and 2,4,6-Triphenyl-1-hexene show very high absorption (>90%), however, low water solubility indicates potential limitations of actual bioavailability though high membrane permeability.

The distribution of compounds shows that sacubitril and most glycoside compounds have the permeability of BBB and CNS is low, so it is less likely to cause neurological side effects. Hallacton B has a relatively high VDSS but still shows minimal CNS penetration, which indicates a wide distribution in peripheral tissues without accumulation in the brain. In contrast, Epiafzelechin 3-O-gallate exhibits high permeability of BBB and CNS, indicating the penetration ability of the central nervous system that potentially increases the risk of neurological side effects, although it can be beneficial for certain indications.

In the metabolic aspect, almost all test compounds did not inhibit CYP2D6 or CYP3A4, shows a relatively low risk of drug interaction. In contrast, sacubitrile and 2,4,6-Triphenyl-1-hexene is predicted to be a CYP3A4 inhibitor, potentially elicit pharmacokinetic interactions on use A combination of therapies.

Excretion predictions show variations in the rate of elimination between compounds. Sacubitril and 2,4,6-Triphenyl-1-hexene has a high total clearance, indicating rapid elimination, whereas Hallacton B and glycoside compounds shows low to moderate clearance that can extend the half-life. All compounds are not interacts with the renal

transporter OCT2, so the risk of nephrotoxicity due to transporter competition is relative minimal.

The toxicity aspect shows significant differences. Sacubitril is predicted to be Ames-toxic and hepatotoxic, while Hallacton B, Isocytisoside, and Vitexin 4"-O-rhamnoside exhibit a safety profile best with negative results on Ames test and hepatotoxicity. Epiafzelechin 3-O-gallate shows potential Ames toxicity, while 2,4,6-Triphenyl-1-hexene exhibits potential hepatotoxicity, which becomes The main limitation of its development.

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Protein Analysis

Ramachandran's plot is one of the main parameters in the evaluation of the quality of three-dimensional protein structures, especially to assess the reasonableness of the torque angle of the protein backbone, namely the phi (φ) and psi (ψ) angles of each amino acid residue. This analysis is particularly important because the conformation of the protein backbone that is not sternally matched can indicate structural modeling errors.

Based on the results of the analysis of the structure of 5jmy protein, a total of 1392 residues were obtained, consisting of 1264 non-glycine and non-proline residues, 82 glycine residues, and 44 proline residues. Of the non-glycine and non-proline residues, as many as 1185 residues (93.8%) were in the most favoured regions, which are the most energetically and sterically stable conformational regions. This percentage exceeds the generally accepted quality threshold of >90%, indicating that the structure model is of excellent quality. A total of 77 residues (6.1%) were in additional permitted regions, which are still structurally acceptable and are often found in natural proteins. There were no residues in generously allowed regions (0.0%), indicating no conformation approaching the instability limit. Only 2 residues (0.2%) were in disallowed regions, a very small amount and still acceptable in the evaluation of the structure of large complex proteins. The relatively flexible distribution of glycine residues and proline which has a torque angle limitation have also been separated in this analysis, so they do not affect the standard residue assessment. Taking into account that high-quality reference structures at ≥2.0 Å resolution and R-factor ≤20% generally have >90% residues in the most preferred regions, then the 5jmy structure can be categorized as a protein model with excellent stereochemical quality.

Overall, the results of Ramachandran's plot show that the conformation of the protein backbone has been properly modeled, sterically stable, and suitable for further analysis such as ligand interaction studies, molecular dynamics simulations, and interpretation of biological mechanisms

CONCLUSION

1. The molecular docking method used is declared valid, as evidenced by the RMSD value of 1.303 Å (≤ 3 Å) of the natural ligand redocking results, so that the docking

parameters can be used for Analysis of test compounds.
2. The grid box setting is at the coordinates x = −20.579; y = 3,317; z = 37,541 with a size of 40 × 40 × 40, which is able to optimally represent the active side of the neprilysin receptor.
3. The docking results showed that the entire test compound could interact with the neprilysin receptor, however, Hallacton B had the most stable bond energy among the test compounds (−9.45 kcal/mol) and values the inhibition constant (Ki) is relatively low (117.49 μM).
4. Hallacton B shows similarity of important interaction residues with sacubitril's positive control ligand, especially in residues of PHE544, VAL580, MET579, TRP693, and HIS711, which indicate similar binding mechanism on the active side of proteins.
5. Based on Lipinski's Rule of Five, Hallacton B meets most of the physicochemical criteria of oral drugs compared to other test compounds, so it has the potential to have better bioavailability.
6. ADMET evaluation shows that Hallacton B has the best safety profile, marked with negative results on Ames test and hepatotoxicity, does not inhibit the enzyme CYP2D6 and CYP3A4, as well as having good peripheral distribution although intestinal absorption is relatively low.
7. Ramachandran's plot analysis showed that 93.8% of the protein residues were at the most favoured regions and only 0.2% are in disallowed regions, so the protein structure of neprilysin has Excellent stereochemical quality and suitable for use in docking studies.
8. Overall, Hallacton B is designated as the best compound and has the most potential as candidate for neprilysin inhibitors from star fruit, and is worthy of further development through Structural optimization and in vitro and in vivo tests.

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REFERENCES

Nugroho, A. A., dkk. (2023). Molecular Docking and ADMET Prediction Studies of Flavonoids as Multi-target
Agents in COVID-19 Therapy: Anti-inflammatory and Antiviral Approaches. Indonesian Journal of
Pharmacy, 34(4), 651–664. doi:10.22146/ijp.4126
Hasan, R., dkk. (2023). Molecular Docking and Pharmacokinetic Prediction of Potential Compounds from Luffa
acutangula as Antidiabetic Candidates. PHARMACY: Jurnal Farmasi Indonesia, 20(1), 71–76.
doi:10.30595/pharmacy.v0i0.16066
Yuni Fatisa, dkk. (2025). Studi Molecular Docking dan Evaluasi Farmakokinetik Senyawa Analog Pirazol

Turunan Benzen-Sulfonilurea sebagai Inhibitor Enzim Aldose Reduktase dan α-Glukosidase Menggunakan
Pendekatan In Silico. Jurnal Riset Kimia, 15(2), artikel 633. doi:10.25077/jrk.v15i2.633
Effendi, N., dkk. (2024). In Silico ADME-T dan Molekular Docking Analog Tamoxifen sebagai Kandidat Agen
Terapi Kanker Payudara. Media Farmasi. Artikel 3305.
Suwardi, S., dkk. (2024). Virtual Screening, Pharmacokinetic Prediction, Molecular Docking and Dynamics
Approaches in the Search for Selective and Potent Natural Molecular Inhibitors of MAO-B. Indonesian
Journal of Chemistry and Environment, 6(2), artikel 68338. doi:10.21831/ijoce.v6i2.68338
Ramadanti, N. A., dkk. (2024/2025). Pharmacophore Modeling, Molecular Docking, and ADMET Approach for
Identification of Anti-Cancer Agents Targeting the C-Jun N-Terminal Kinase (JNK) Protein. EKSAKTA:
Berkala Ilmiah Bidang MIPA, Vol.24-Iss.01, artikel 391.
Rahmadani, dkk. (2025). Analisis Lipinski Rule of Five pada Senyawa Flavonoid. Indonesian Journal of
Pharmaceutical Education (e-Journal), 5(3), 343–356.
Nugroho, A. A., dkk. (2023). Molecular Docking and ADMET Prediction Studies of Flavonoids as Multi-target
Agents in COVID-19 Therapy: Anti-inflammatory and Antiviral Approaches. Indonesian Journal of
Pharmacy, 34(4), 651–664. doi:10.22146/ijp.4126
Hasan, R., Herowati, R., dkk. (2023). Molecular Docking and Pharmacokinetic Prediction of Potential
Compounds from Luffa acutangula as Antidiabetic Candidates. PHARMACY: Jurnal Farmasi Indonesia,
20(1), 71–76. doi:10.30595/pharmacy.v0i0.16066
Yuni Fatisa, Utami., dkk. (2025). Studi Molecular Docking dan Evaluasi Farmakokinetik Senyawa Analog Pirazol Turunan Benzen-Sulfonilurea sebagai Inhibitor Enzim Aldose Reduktase dan α-Glukosidase Menggunakan
Pendekatan In Silico. Jurnal Riset Kimia, 15(2), artikel 633. doi:10.25077/jrk.v15i2.633
Effendi, N., dkk. (2024). In Silico ADME-T dan Molekular Docking Analog Tamoxifen sebagai Kandidat Agen Terapi Kanker Payudara. Media Farmasi. Artikel 3305.
Suwardi, S., dkk. (2024). Virtual Screening, Pharmacokinetic Prediction, Molecular Docking and Dynamics
Approaches in the Search for Selective and Potent Natural Molecular Inhibitors of MAO-B. Indonesian
Journal of Chemistry and Environment, 6(2), artikel 68338. doi:10.21831/ijoce.v6i2.68338
Ramadanti, N. A., dkk. (2024/2025). Pharmacophore Modeling, Molecular Docking, and ADMET Approach for
Identification of Anti-Cancer Agents Targeting the C-Jun N-Terminal Kinase (JNK) Protein. EKSAKTA:
Berkala Ilmiah Bidang MIPA, Vol.24-Iss.01, artikel 391.
Immanuela, J. F., dkk. (2023). Epidemiolgi Deskriptif Hipertensi di Puskesmas Arjasa Kabupaten Jember. Sehat
Rakyat: Jurnal Kesehatan Masyarakat, 2(1), 148-159.

Akbar, N. A., dkk. (2022, December). Studi in Silico Senyawa Yang Terkandung Dalam Tanaman Daun Sirih
Merah (Piper crocatum RUIZ & PAV) Sebagai . Kandidat Anti SARS Cov-2 In Prosiding Seminar Nasional
Diseminasi Hasil Penelitian Program Studi S1 Farmasi (Vol. 2, No. 1).
Jitayu Sekarininta Mumpun, dkk. (2021) Perbandingan Efektivitas Sacubitril/Valsartan dengan Enalapril pada
Pasien Gagal Jantung: Literature review
Gede Ngurah Hadi Chandra, I Made Adnyana Partha Wijaya. (2021). Molecular DockingKaempferol sebagai
Antiinflamasi pada Aterosklerosissecara In Silico. Jurnal Ilmiah Medicamento : Universitas Udayana,
Denpasar, Bali. Vol.7.No.
Hari Hariadi, dkk. (2022) Pengaruh penambahan ekstrak bunga telang (Clitoria ternatea L) sebagai minuman
fungsional antihipertenasi, Vol. 4, hlm 1-6
Algiza Gauthfa, dkk. (2025) Interprofessional Collaboration dalam Upaya Penanganan dan Pencegahan
Hipertensi Melalui Penyuluhan di Kelurahan Margawati
Ma'rifatul Lailatus Zahro, dkk. (2025) Hubungan Efikasi Diri Dengan Kekambuhan Pada Pasien Hipertensi Di
Posbindu Desa Senduro Di wilayah UPT. Puskesmas Senduro

TABLE AND FIGURE

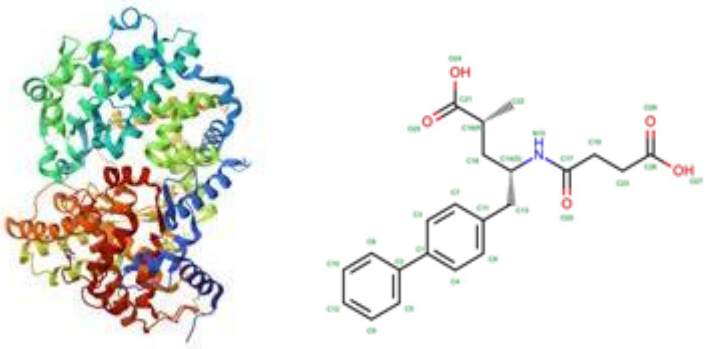

Figure1. Reseptor Neprilysin-3D and Native Ligan (PDB IDE 5jmy)
https://doi.org/10.2210/pdb5JMY/pdb

Table 1. Grid Box Setup

PDB ID	Koordinat			Point			RMSD
	x	y	z	x	y	z	
5JMY	-20,579	3.317	37.541	40	40	40	1.303

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RESEARCH ARTICLE OPEN ACCESS

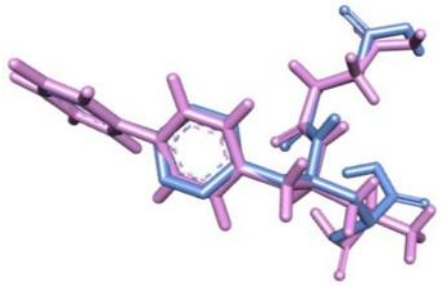


Figure 3. Results before natural ligand docking validation (blue) and after docking validation (purple)

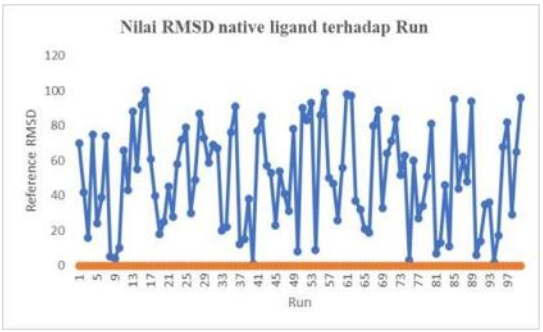


Figure 4. Graphic: RMSD native ligand

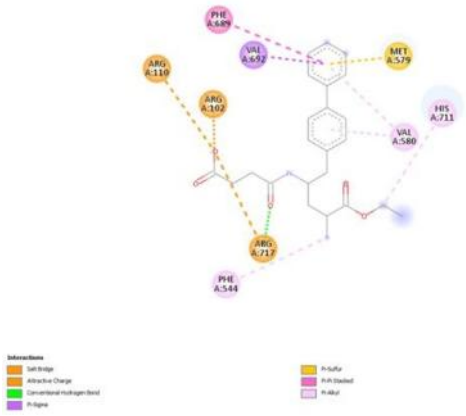
Table 2. Molecular Docking Results

Compound Name	RMSD (A)	Energy Bonding (kcal/mol)	Konstanta Inhibisi (uM)	Amino Acids	Types of Bonds
Sacubitril	35.940 A	-11.36	4.71	**PHE A : 689**	Hydrophbic
				PHE A : 544	Hydrophbic
				VAL A : 692	Hydrophbic
				VAL A : 580	Hydrophbic
				MET A :579	Hydrophbic
				ARG A :102	Hydrophbic
				ARG A :110	Hydrophbic
				ARG A :717	Hydrophbic
				HIS A : 711	Hydrophbic
Isocytisoside	35.911 A	-9.19	182.28	ALA A : 543	Hydrogen
				GLU A : 646	Hydrogen
				ARG A :717	Hydrogen
				TRP A : 693	Hydrogen
				PHE A : 689	Hydrogen
				GLU A : 584	Hydrophobic

				VAL A : 580	Hydrophobic
				VAL A : 692	Hydrophobic
				MET A :579	Hydrophobic
				HIS A : 583	Hydrophobic
Hallacton B	52.761 A	-9.45	117.49	ASN A : 542	Hydrogen
				HIS A : 587	Hydrogen
				GLU A : 646	Hydrogen
				GLU A : 584	Hydrogen
				PHE A : 544	Hydrophobic
				PHE A : 106	Hydrophobic
				VAL A : 580	Hydrophobic
				MET A :579	Hydrophobic
				TRP A : 693	Hydrophobic
				HIS A : 711	Hydrophobic
Vitexin 4"-o-rhamnoside	42.915 A	-8.84	330.69	ARG A :102	Hydrogen
				ASN A : 542	Hydrogen
				ASP A : 709	Hydrogen
				VAL A : 580	Hydrogen
				HIS A : 583	Hydrogen
				MET A :579	Hydrophobic
				PHE A : 689	Hydrophobic
				ARG A: 717	Hydrophobic
				TRP A : 693	Hydrophobic
				GLU A: 646	Hydrophobic
Epiafzelechin 3-O-gallate	36.678 A	-9.42	123.79	ASP A : 709	Hydrogen
				ARG A :102	Hydrogen
				ARG A :717	Hydrogen
				MET A :579	Hydrogen
				GLU A : 584	Hydrogen
				PHE A : 544	Hydrogen
				VAL A : 580	Hydrophobic
				GLU A : 646	Hydrophobic
				HIS A : 587	Hydrophobic
				HIS A : 711	Hydrophobic

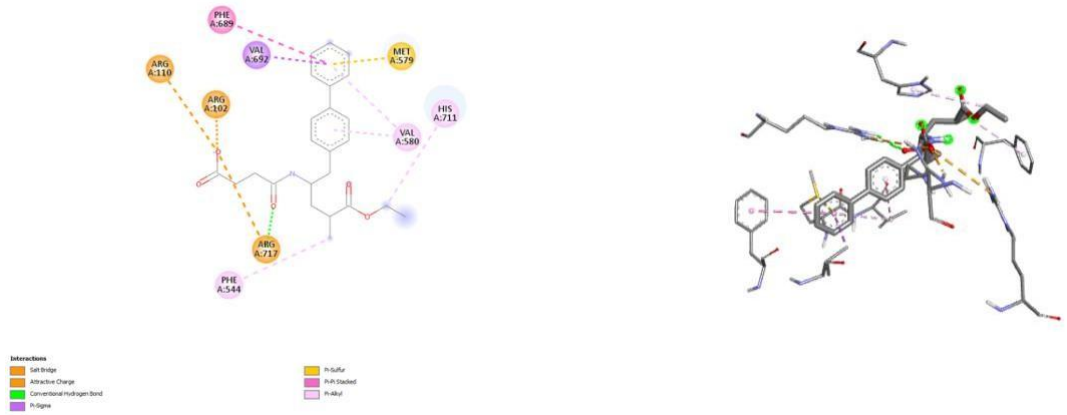
2,4,6 Triphenyl-1-hexene	42.604 A	-9.01	250.57	**HIS A : 711**	Hydrophobic
				HIS A : 583	Hydrophobic
				PHE A: 106	Hydrophobic
				VAL A:580	Hydrophobic
				ALA A:543	Hydrophobic
				ARG A:717	Hydrophobic
				GLU A:584	Hidrofobik

Remark: The amino acid residue is the same between the positive control and the test compound indicated by the bold printed



e 4. Relationship Between Medication Adherence with Blood Pressure Control

Medication Adherence	Uncontrolled	Controlled	Total	p value
Non-adherent	50	5	55	0,445
Adherent	4	1	5	
Total	**54**	**6**	**60**	



A. Ligan 1 (Sacubitril)

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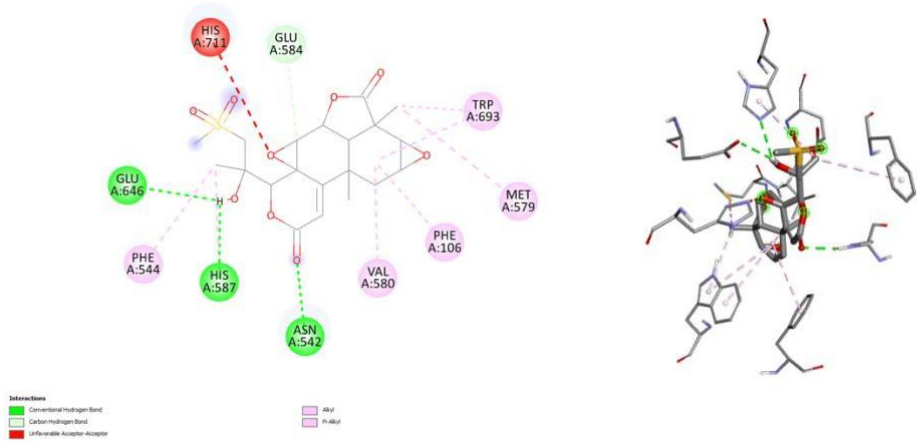
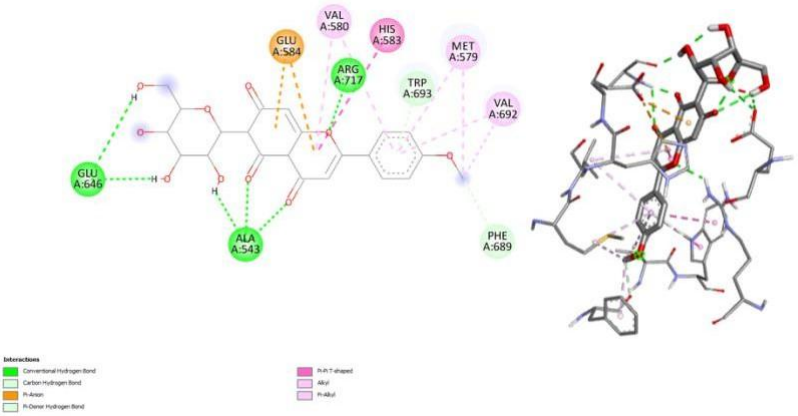


B. Ligan 9 (Isocytisoside)



C. Ligan 2 C (Hallacton B)