BIOLOGY, MEDICINE, & NATURAL PRODUCT CHEMISTRY ISSN 2089-6514 (paper)
Volume 14, Number 1, April 2025 | Pages: 275-282 | DOI: 10.14421/biomedich.2025.141.275-282 ISSN 2540-9328 (online)

In Silico Analysis of Ocimum Basilicum Flavonoids as Natural Antihypertensive Agent on Angiotensin II Type-1 Receptor (AT1R)

Amir Thalib[1,*], Irma Putri Damayanti[2]
[1]Department of Medicine; [2]Department of Herbal Medicine, Faculty of Medicine; University of Muhammadiyah Purwokerto, Jl. KH. Ahmad Dahlan, Purwokerto 53182, Tel. +62-856-2988-092, Indonesia.

Corresponding author*
amirthalib18@gmail.com

Manuscript received: 28 February, 2025. Revision accepted: 20 May, 2025. Published: 24 June, 2025.

Abstract

Despite the efficacy of antihypertensive medications like ARBs, their adverse effects frequently result in suboptimal adherence. This study investigates the efficacy of flavonoids obtained from herbal sources as natural substitutes for traditional antihypertensive therapies. This study employed *in silico* molecular docking to examine the binding affinity of flavonoids to the angiotensin II type-1 receptor (AT1R) in comparison to standard angiotensin receptor blockers (ARBs), namely Eprosartan, Azilsartan, Irbesartan, Telmisartan, Valsartan, Losartan, Olmesartan, and Candesartan. Docking analysis indicated that the flavonoids exhibited a favorable binding affinity of -8.8 kcal/mol for AT1R. Moreover, ADME and toxicity assessments indicated that flavonoids exhibit advantageous pharmacokinetics and minimal toxicity, with no significant adverse interactions anticipated with primary metabolic enzymes. The structural validation, encompassing Ramachandran plots and ERRAT analysis, affirmed the reliability of the modeled AT1R protein, achieving a quality score of 97.13%. This study concludes that flavonoids derived from *Ocimum basilicum* exhibit significant potential as natural antihypertensive agents. These findings may facilitate the development of plant-based therapies with minimal adverse effects, enhance treatment adherence, and improve the pharmacological options for managing hypertension.

Keywords: ADME; Angiotensin II receptor; Flavonoids; Molecular docking; Ocimum Basilicum.

Abbreviations: ARBs: angiotensin receptor blockers; ACE: Angiotensin-converting enzyme; AT1R: angiotensin II type-1 receptor; ADME: absorption, distribution, metabolism, and excretion; VDss: volume of steady-state distribution.

INTRODUCTION

Hypertension is a multifactorial condition and is an important risk factor for stroke and cardiovascular disease (Raddaoui et al., 2024). Approximately 33% of the global population of 8 billion individuals suffers from hypertension. Lifestyle modifications are essential for the prevention and management of hypertension, and both governmental and industrial support are crucial for the endorsement and implementation of these modifications (Charchar et al., 2024).

Angiotensin II type-1 receptor blockers (ARBs) are extensively prescribed medications for managing arterial hypertension, heart failure, and chronic kidney disease (de Vries, 2020). Nonetheless, antihypertensive medications continue to exhibit numerous side effects, necessitating the substitution of these drugs with alternatives that possess minimal adverse effects. Previous research by RuiJun Chen et al (2021) examining the side effects of anti-hypertensive medications, particularly ACE inhibitors and ARBs, indicates that there is no significant difference between these two classes regarding the risk of acute myocardial infarction, heart failure, stroke, or composite cardiovascular events (Chen et al., 2021).

Medicinal herbs remain a viable alternative treatment for various diseases, including cardiovascular diseases (CVDs). There is an unparalleled impetus for the utilization of herbal Preparations in contemporary medicinal systems, this initiative is driven by multiple factors, foremost among them being their cost therapeutic potential relative to conventional modern treatments and the general understanding of their safety (Shaito et al., 2020).

The side effects associated with antihypertensive medications, including fatigue, myalgia, and insomnia, frequently serve as a substantial predictor of inadequate adherence to treatment (Mitkova et al., 2024). Consequently, alternative medicine, specifically herbs, is regarded as a traditional treatment that may support or replace conventional medicine.

Flavonoids are small molecular secondary metabolites produced by plants that exhibit diverse biological activities (Mierziak et al., 2014). Flavonoids

are prevalent in numerous plant species (Ysrafil et al., 2023). Flavonoids are a prevalent and extensive category of plant secondary metabolites characterized by hydroxylated phenyl rings, encompassing flavones, catechins, and anthocyanins. A diverse array of hydroxylation, methoxylation, glycosylation, and oligomerization patterns has been documented for this class of compounds, with thousands of distinct polyphenol structures reported in the literature. Polyphenols captivate the scientific community owing to their diverse biological activities, including advantages for cardiovascular health (Joyner, 2021).

Hypertension induces oxidative stress, resulting in vasoconstriction (Matsubara, 1998). Flavonoids can induce vasodilation by enhancing nitric oxide (NO) activity in endothelial cells. These flavonoids may inhibit AT1R; however, their precise affinity and interaction with AT1R remain undetermined. AT1R is located in the heart, brain, adrenal glands, kidneys, and liver (Kumar & Pandey, 2013). AT1R comprises 359 amino acids and has a molecular weight of 4 kDa. The amino acid residues Arg167 and Tyr35 are involved in the interaction between ARB drugs and AT1R (Miura, 2011).

Evaluating the efficacy of flavonoids as substitutes for ACE inhibitors (ACEi) and Angiotensin Receptor Blockers (ARB) using *in silico* molecular docking with the angiotensin II type 1 receptor (AT1R) target protein. This study attempts to analyze the interaction and binding affinity of flavonoids to AT1R in comparison to conventional ACE inhibitors and angiotensin receptor blockers, as a foundation for the development of antihypertensive therapies based on natural compounds.

MATERIALS AND METHODS

Study area

For Molecular docking process, this study used a computer with specifications Intel(R) Celeron(R) N4020 CPU @ 1.10GHz, 1101 Mhz, 2 Core(s), 2 Logical Processor(s), 4 GB RAM, and operating system: Microsoft Windows 11 Home Single Language (10.0.22631 Build 22631) BIOS:DVCN17WW

Procedures

Preparation and Ligands

The test compounds used are bioactive compounds sourced from the majority of plants that grow in Indonesia, Malaysia, Thailand and other Asian countries, namely flavonoids (de Vries, 2020). Numerous Angiotensin Receptor Blockers (ARB) medications were utilized to evaluate and compare their binding affinity to flavonoids (Hermida et al., 2011). Utilizing their canonical SMILES as the input and The two-dimensional and three-dimensional structures of the chosen ligands and protein were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) in SDF format (Sri Prakash et al., 2023). Comprehending the molecular mechanisms that regulate bioactivity and forecasting potential side effects or cross-reactivity necessitates the identification of phytochemical targets. Swiss Target Prediction(http://www.swisstargetprediction.ch/) analyzes ligand configurations against known drugs to identify protein targets. The assessed phytochemicals' targets related to a specific drug are identified via Swiss Target Prediction (Gfeller et al., 2014). Among various candidate proteins that interact with flavonoids, we selected the Type-1 angiotensin II receptor (AT1R) as the target to evaluate its binding affinity and to compare it with the binding affinities of ACE and ARB.

Target selection and validation

AT1R was selected as the protein of interest for the study. The SWISS-MODEL (https://swissmodel.expasy.org/) was utilized to predict the three-dimensional structure of the AT1R protein (Ali et al., 2024). subsequently conducted protein validation utilizing PROCHECK and ERRAT using SAVES (https://saves.mbi.ucla.edu/) (Deka et al., 2015; Mariana et al., 2023). PyMOL (https://pymol.org/2/) is used for three-dimensional visualization of proteins and the receptor was modified by the removal of water (Putra et al., 2024).

Docking molecules

Docking study was conducted using AutoDock Vina in PyRx software (https://pyrx.sourceforge.io/), Throughout the docking phase, the ligands were regarded as flexible (Prasanth et al., 2021). The molecular docking results of the protein-ligand interaction were analyzed using the PyMOL software (Uma Maheswari & Sankar, 2024).

Data analysis

Drug development entails the evaluation of absorption, distribution, metabolism, and excretion (ADME) at progressively earlier stages of the discovery process, when numerous compounds are under consideration but access to physical samples is restricted. A potent molecule must arrive at its target. Achieve adequate concentration within the body and maintain a bioactive state for an extended duration for the expected biological event to transpire to be efficacious as a pharmaceutical agent. For this purpose, ADME analysis for flavonoids is delineated by the SWISSADME online platform (http://www.swissadme.ch) (Daina et al., 2017; Ismail et al., 2023). next to docking, the next process involves predicting the toxicity status of the natural ligands (flavonoids) utilizing the 'ProTox-III' web server (https://tox.charite.de/protox3/) (Tithi et al., 2023).

RESULTS AND DISCUSSION

Ligands and Protein identification

The docking process commences with the compilation of a database of herbal compounds from *Ocimum basilicum*,

identifying one active compound from the *Ocimum basilicum* family that exhibits anti-hypertensive properties associated with the Type-1 angiotensin II receptor, specifically Flavonoids. Additionally, the ligand structure is generated utilizing PubChem in SDF format.

The macromolecules utilized in this study are Type-1 angiotensin II receptor. This study pertains to the Type-1 angiotensin II receptor downloaded from the Protein Data Bank (PDB). Receptors generally comprise water molecules and residues. Consequently, water molecules and residues must be eliminated, require preparation with PyMOL software to avoid disruption during the docking procedure.

This study employs comparative analysis of ARB class drugs, specifically Eprosartan, Azilsartan, Irbesartan, Telmisartan, Valsartan, Losartan, Olmesartan, and Candesartan as ligands, which will be evaluated against flavonoids to assess their binding affinity to the Type-1 angiotensin II receptor (Figure 1.).

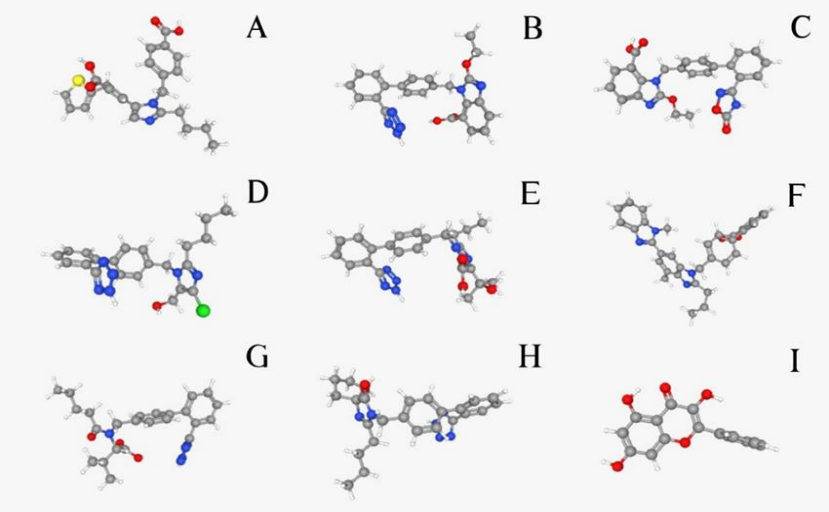

Figure 1. Visualization of ligands. (A) Eprosartan; (B) Candesartan; (C) Azilsartan; (D) Losartan; (E) Olmesartan; (F) Telmisartan; (G) Valsartan; (H) Irbesartan; (I) Natural ligand Flavonoids.

Structure validation of modeled proteins

Validation is employed to verify the reliability of the protein structure for docking. The protein structure validation was conducted utilizing the PROCHECK Ramachandran plot and ERRAT (Hamid et al., 2021).

ERRAT

ERRAT assesses the model using statistics to evaluate unbound interaction relationships among various atom types, where elevated scores signify superior quality. ERRAT also delivers results with overall significance and quality, with a widely accepted score exceeding 50, indicating a stable protein (Sumitha et al., 2020).

The ERRAT analysis results (Figure 2) indicated that the quality factor values were 97.134% for the angiotensin II type-1 receptor (AT1R). The outcome of this computation indicates that the Protein structure of the angiotensin II type-1 receptor (AT1R), characterized by high quality and high resolution.

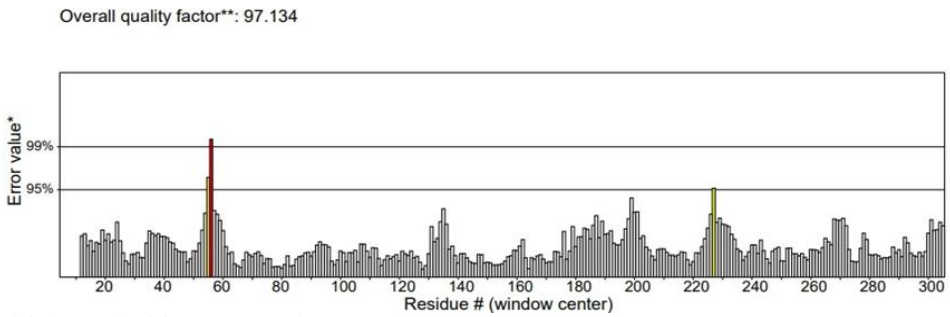

Figure 2. Structure Validation result of the ERRAT Tool.

Ramachandran plots

PROCHECK inspection by Ramachandran plots (Figure 3.) focuses on specific geometries and allows the overall structure to be evaluated. The Ramachandran plot illustrates the distribution of the torsional angles φ (phi) and ψ (psi) of the protein's main chain. To see if the

Ramachandran plot is good for protein structure analysis, it can be checked by plotting non-glycine residues in disallowed regions less than 0.8% (Gunasekaran et al., 1996).

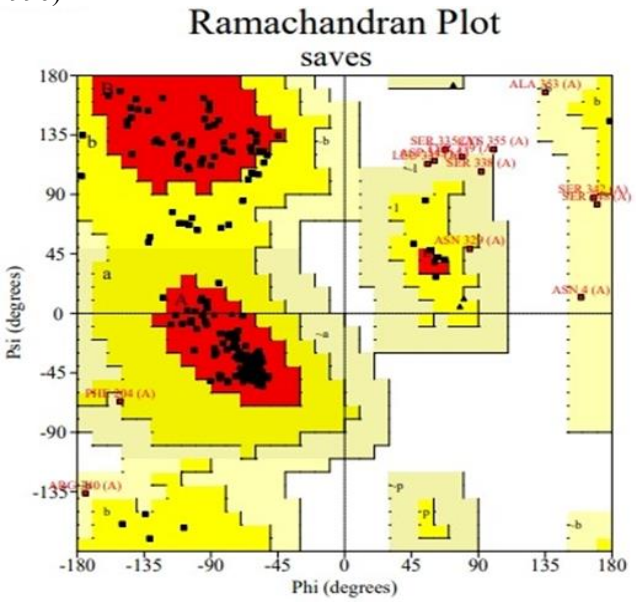

Figure 3. The Ramachandran PROCHECK determined the plot. Red represents a preferred region, yellow indicates an authorized region, bright yellow suggests an amino acid region that is liberally allowed, and white indicates a banned region.

The results show that 87.5% of the residues are in the most favorable region, which indicates adequate structural stability. 8.5% of the residues were in the additional allowed region, and 3.4% were in the general allowed region. 0.6% of the residuals were in the non-allowed region, indicating potential local instability or possible modeling errors. Overall, the structure is close to the criteria of a high-quality model, although further refinements may be needed to improve its validity.

Molecular docking

Docking was conducted on one active compound of *Ocimum basilicum* with the AT1R receptor, utilizing Eprosartan, Azilsartan, Irbesartan, Telmisartan, Valsartan, Losartan, Olmesartan, and Candesartan ligands for comparison. Docking is performed using the PYRX, AutoDock, and Vina software, followed by the configuration of the grid box. The binding affinity served as the primary criterion for assessing the quality of the molecular docking outcomes (Agu et al., 2023).

The results indicated that the natural ligands of flavonoids indicate spontaneous binding to the Type-1 angiotensin II receptor, showing a binding affinity of -8.8 kcal/mol. In comparison, the binding affinities of the following agents are as follows: Valsartan -6.8 kcal/mol, Eprosartan -8.2 kcal/mol, Losartan -8.5 kcal/mol, Olmesartan -9.5 kcal/mol, Irbesartan -9.9 kcal/mol, Candesartan -10.2 kcal/mol, Azilsartan -10.4 kcal/mol, and Telmisartan -11.2 kcal/mol (Table 1). Molecular docking results indicate that *Ocimum basilicum* possesses the potential to treat hypertension.

Table 1. Result of molecular docking simulation of ligands against AT1R.

Ligands	CID	Molecular Formula	Molecular Weight (g/mol)	Binding Affinity (Kcal/mol)
Flavonoids	5281616	C15H10O5	270.24	-8.8
Valsartan	60846	C24H29N5O3	435.5	-6.8
Eprosartan	5281037	C23H24N2O4S	424.5	-8.2
Losartan	3961	C24H26N6O3	446.5	-9.5
Olmesartan	158781	C24H26N6O3	446.5	-9.5
Irbesartan	3749	C25H28N6O	428.5	-9.9
Candesartan	2541	C24H20N6O3	440.5	-10.2
Azilsartan	135415867	C25H20N4O5	456.4	-10.4
Telmisartan	65999	C33H30N4O2	514.6	-11.2

Post-docking analysis

The molecular docking results generated by PyRx software will be subsequently visualized with PyMOL to assess the ligand's positioning within the receptor's active site. This visualization attempts to identify significant interactions between the ligand and essential residues on the receptor. Furthermore, an analysis of particular interactions, including hydrogen bonds, hydrophobic interactions, and various bond types, will be conducted utilizing the ProteinPlus website, which offers comprehensive information on residues involved in ligand-receptor interactions. According to the photos provided above, the interactions depicted in each image are as follows: Figure A illustrates hydrogen bonds between Tyr (hydroxyl) and Arg residues, alongside π-π interactions involving the aromatic rings of Trp and Tyr residues. Figure B illustrates hydrogen connections between the ligand and arginine residues, and hydrophobic interactions between the ligand's aromatic ring and aromatic residues. Figure C illustrates a hydrogen bond with the Tyr residue and a π-π contact between the aromatic ring of the residue and the ligand. Figure D illustrates hydrogen bonds with Tyr and Val residues, along with π-π interactions involving Trp residues. Figure E illustrates the interaction comprising hydrogen bonds with Ser and Phe residues, as well as

hydrophobic interactions between the ligand and aromatic residues. Image F depicts hydrogen bonding with the tyrosine residue and hydrophobic contact with the residue's aromatic ring. Figure G illustrates hydrogen bonding with Thr and Tyr residues, together with π-π interactions involving aromatic residues. In Figure H, interactions comprise hydrogen bonds with aspartate residues and π-π interactions between the ligand and aromatic residues. Ultimately, in Figure I, hydrogen bonds are formed with Tyr residues, and hydrophobic interactions occur between the ligand and aromatic residues. The interplay of these interactions demonstrates how hydrogen bonds, π-π interactions, and hydrophobic interactions influence the ligand's stability with respect to the protein in each figure (Figure 4.).

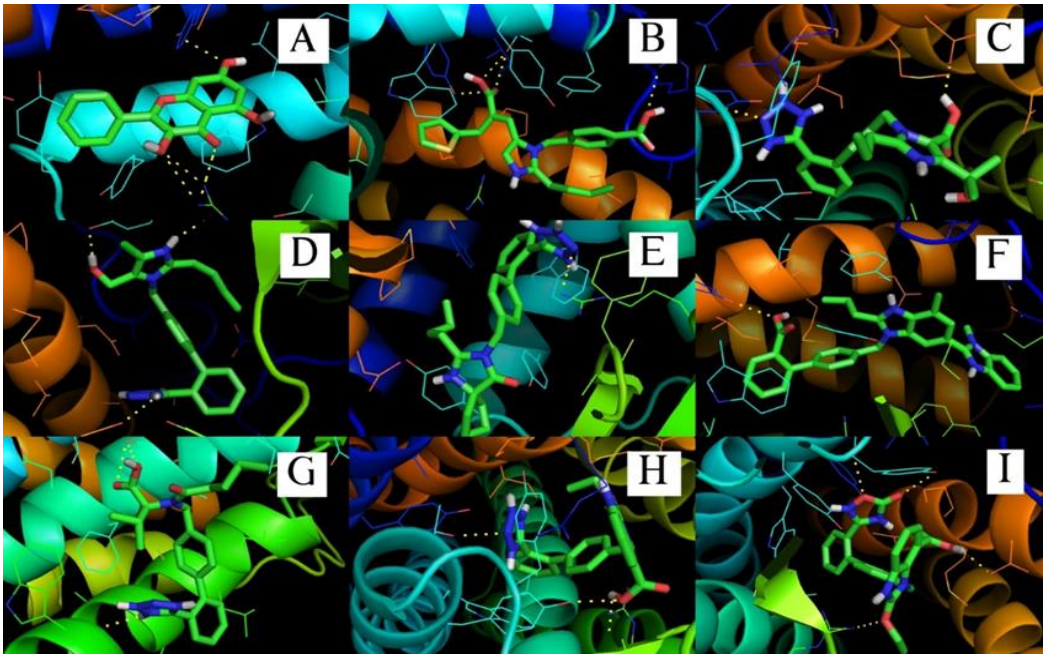

Figure 4. The Ramachandran PROCHECK determined the plot. Red represents a preferred region, yellow indicates an authorized region, bright yellow suggests an amino acid region that is liberally allowed, and white indicates a banned region.

In silico drug-likeness and toxicity predictions

Subsequent to molecular docking analyses, the absorption, distribution, metabolism, elimination, and toxicity (ADMET) of flavonoids natural compound ligands were evaluated using the SwissADME (http://www.swissadme.ch/) and ProTox-3.0 (https://tox.charite.de/protox3/) platforms to forecast their significant pharmacokinetic characteristics. ADMET properties encompass absorption metrics such as Caco-2 permeability, aqueous solubility, human intestinal absorption, P-glycoprotein substrates, P-glycoprotein inhibitors I and II, and dermal permeability; distribution factors including volume of steady-state distribution (VDss), unbound fraction, blood-brain barrier (BBB) permeability, and central nervous system (CNS) permeability; metabolic considerations like cytochrome P450 inhibition and CYP2D6/CYP3A4 substrate status; excretion parameters such as renal OCT2 substrate and total drug clearance; and toxicity assessments including Rat LD50, AMES test results, T. pyriformis toxicity, small fish toxicity, maximum tolerated dose, chronic oral toxicity in rats, hepatotoxicity, skin sensitization, and hERG inhibitors I and II. Drug similarity characteristics were forecasted by submitting the structures of chosen phytochemicals in SMILES format (Vardhan et al., 2020).

The ADME analysis (Figure 5.) findings for the Compound, which has a molecular formula of C15H10O5 and a molecular weight of 270.24 g/mol, indicate that its physicochemical properties make it suitable for further development as a drug candidate. The heavy atom count of 20 and TPSA of 90.90 Å² show that the molecular structure is stable and has good membrane penetration ability. The compound's LogP falls between 2.08 and 2.58, indicating an equilibrium between water and lipid solubility that is crucial for pharmacokinetics. The compound has moderate solubility in water based on different techniques, such as Log S ESOL: -3.46.

Regarding pharmacokinetics, the substance is easily absorbed in the gastrointestinal tract, yet cannot pass through the blood-brain barrier, therefore the chances of negative impacts on the central nervous system are expected to be minimal. Nevertheless, the compound may block CYP1A2, CYP2D6, and CYP3A4 enzymes, thus requiring increased focus on potential interactions with other medications processed through this pathway. The skin permeability is poor, indicated by a Log Kp value of -6.35 cm/s.

Assessment of drug likeness indicated that this compound adhered to key guidelines such as Lipinski, Ghose, Veber, Egan, and Muegge without any breaches, with a bioavailability score of 0.55. In terms of medicinal chemistry, this compound exhibits no PAINS alerts or lead likeness, indicating high promise as a potential lead in drug development with minimal risk of false positives in biological assays. The compound's polarity profile, lipophilicity, and flexibility are within accepted ranges for promoting biological activity. In general, the compound deserves more research with a focus on its metabolic interactions.

The study's analysis of toxicity resulted in an LD50 value of 3919 mg/kg (Figure 5.). This value shows that the oral dose is lethal for half of the test animal population. The low toxicity classification is based on the relationship between the LD50 value and the level of toxicity risk. The findings of this study indicated a toxicity class of 5. Based on this categorization of toxicity, substances in class 5 have very low toxicity and present little danger when used as directed.

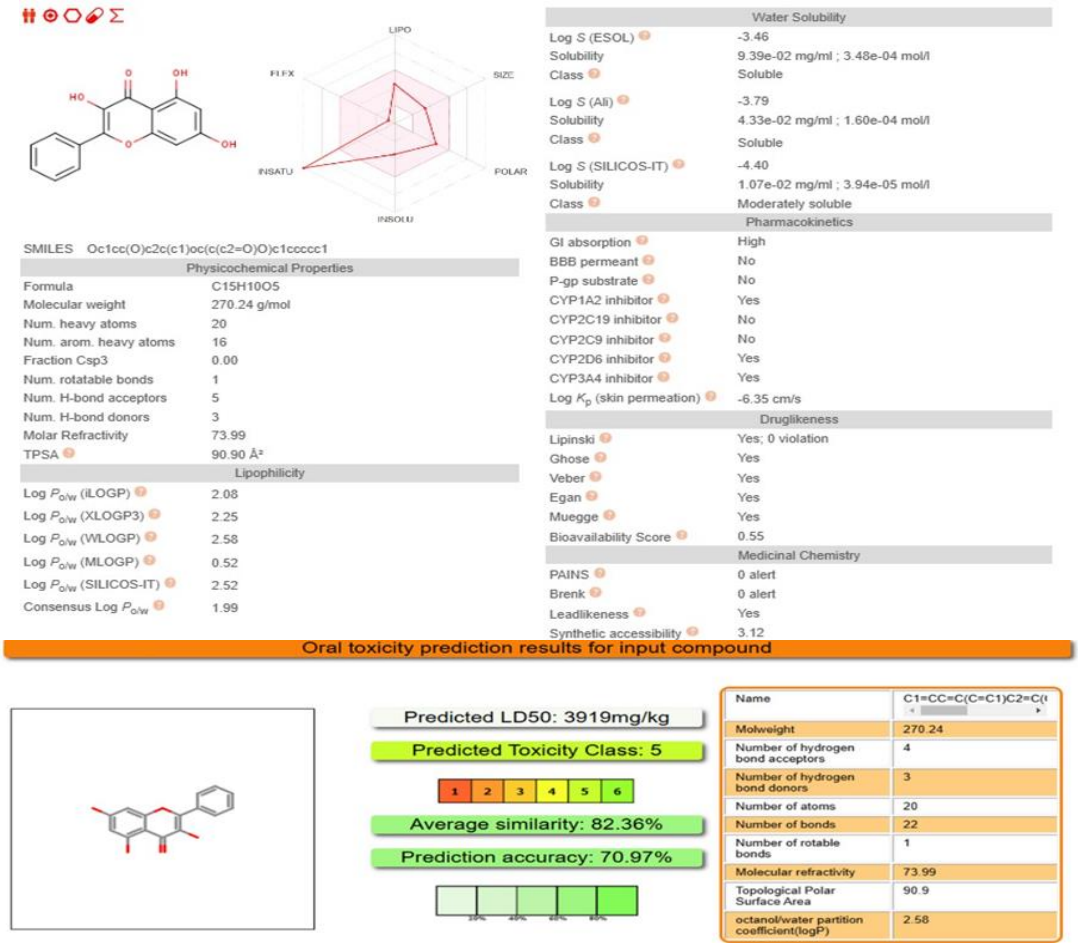

Figure 5. ADMET analysis of flavonoid drugs demonstrating profiles of absorption, distribution, metabolism, excretion, and toxicity. This data is utilized to assess the pharmacokinetic potential and safety of substances in medication development.

CONCLUSIONS

This study highlights the potential of flavonoids as natural alternatives for antihypertensive therapy, focusing on their interaction with the angiotensin II type-1 receptor (AT1R) through *in silico* molecular docking. The findings suggest that flavonoids, derived from *Ocimum basilicum*, exhibit significant binding affinity to AT1R, supporting their role in reducing blood pressure.

Structural validation of the AT1R protein strengthens the reliability of the results. This study provides a basis for developing plant-based antihypertensive agents, encouraging further experimental studies and clinical trials to confirm the efficacy and safety of flavonoids-based therapies. These insights can contribute significantly to advancing personalized and sustainable healthcare solutions.

Acknowledgements: The author thanks to University of Muhammadiyah Purwokerto for the time given to conduct research as well as the provision of computers for docking with the required specifications.

Authors' Contributions: Irma Putri Damayanti designed the study, provided input and supervised the docking. Amir carried out the docking work, analyzed the data And wrote the manuscript. All authors read and approved the final version of the manuscript

Competing Interests: The authors declare that there are no competing interests.

Funding: The authors declare no funding in this research.

REFERENCES

Agu, P. C., Afiukwa, C. A., Orji, O. U., Ezeh, E. M., Ofoke, I. H., Ogbu, C. O., Ugwuja, E. I., & Aja, P. M. (2023). Molecular docking as a tool for the discovery of molecular targets of nutraceuticals in diseases management. *Scientific reports*, *13*(1), 13398. https://doi.org/10.1038/s41598-023-40160-2

Ali, S., Ali, U., Safi, K., Naz, F., Jan, M. I., Iqbal, Z., Ali, T., Ullah, R., & Bari, A. (2024). In silico homology modeling of dengue virus non-structural 4B (NS4B) protein and its molecular docking studies using triterpenoids. *BMC infectious diseases*, *24*(1), 688. https://doi.org/10.1186/s12879-024-09578-5

Charchar, F. J., Prestes, P. R., Mills, C., Ching, S. M., Neupane, D., Marques, F. Z., Sharman, J. E., Vogt, L., Burrell, L. M., Korostovtseva, L., Zec, M., Patil, M., Schultz, M. G., Wallen, M. P., Renna, N. F., Islam, S. M. S., Hiremath, S., Gyeltshen, T., Chia, Y. C., Gupta, A., … Tomaszewski, M. (2024). Lifestyle management of hypertension: International Society of Hypertension position paper endorsed by the World Hypertension League and European Society of Hypertension. *Journal of hypertension*, *42*(1), 23–49. https://doi.org/10.1097/HJH.0000000000003563

Chen, R., Suchard, M. A., Krumholz, H. M., Schuemie, M. J., Shea, S., Duke, J., Pratt, N., Reich, C. G., Madigan, D., You, S. C., Ryan, P. B., & Hripcsak, G. (2021). Comparative First-Line Effectiveness and Safety of ACE (Angiotensin-Converting Enzyme) Inhibitors and Angiotensin Receptor Blockers: A Multinational Cohort Study. *Hypertension (Dallas, Tex. : 1979)*, *78*(3), 591–603. https://doi.org/10.1161/HYPERTENSIONAHA.120.16667

Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific reports*, *7*, 42717. https://doi.org/10.1038/srep42717

de Vries A. A. F. (2020). Renin-angiotensin system inhibition in COVID-19 patients. *Netherlands heart journal: monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation*, *28*(7-8), 396–405. https://doi.org/10.1007/s12471-020-01439-5

Deka, H., Sarmah, R., Sharma, A., & Biswas, S. (2015). Modelling and Characterization of Glial Fibrillary Acidic Protein. *Bioinformation*, *11*(8), 393–400. https://doi.org/10.6026/97320630011393

Gfeller, D., Grosdidier, A., Wirth, M., Daina, A., Michielin, O., & Zoete, V. (2014). SwissTargetPrediction: a web server for target prediction of bioactive small molecules. *Nucleic acids research*, *42*(Web Server issue), W32–W38. https://doi.org/10.1093/nar/gku293

Gunasekaran, K., Ramakrishnan, C., & Balaram, P. (1996). Disallowed Ramachandran conformations of amino acid residues in protein structures. *Journal of molecular biology*, *264*(1), 191–198. https://doi.org/10.1006/jmbi.1996.0633

Hamid, M., Habib, U., Batool, J., Qaisar, A., & Zafar, R. (2021). Identification and computational analysis of 3D-structure of MOCS1. *Research Square*. https://doi.org/10.21203/rs.3.rs-473901/v1

Hermida, R. C., Ayala, D. E., Fernández, J. R., Portaluppi, F., Fabbian, F., & Smolensky, M. H. (2011). Circadian rhythms in blood pressure regulation and optimization of hypertension treatment with ACE inhibitor and ARB medications. *American journal of hypertension*, *24*(4), 383–391. https://doi.org/10.1038/ajh.2010.217

Ismail, H., Khalid, D., Waseem, D., Ijaz, M. U., Dilshad, E., Haq, I. U., Bhatti, M. Z., Anwaar, S., Ahmed, M., & Saleem, S. (2023). Bioassays guided isolation of berberine from Berberis lycium and its neuroprotective role in aluminium chloride induced rat model of Alzheimer's disease combined with insilico molecular docking. *PloS one*, *18*(11), e0286349. https://doi.org/10.1371/journal.pone.0286349

Joyner P. M. (2021). Protein Adducts and Protein Oxidation as Molecular Mechanisms of Flavonoid Bioactivity. *Molecules (Basel, Switzerland)*, *26*(16), 5102. https://doi.org/10.3390/molecules26165102

Kumar, S., & Pandey, A. K. (2013). Chemistry and biological activities of flavonoids: an overview. *TheScientificWorldJournal*, *2013*, 162750. https://doi.org/10.1155/2013/162750

Mariana, M., Abbas, S., Salamiah, S., Soedijo, S., Marsuni, Y., Sepe, M., et al. (2023). In Silico Analysis of Aspergillus Flavus Fungal Proteins: Structural and Functional Insights Using Its Primers. *Pakistan Journal of Phytopathology*. 35(02):397-498. https://doi.org/10.33866/phytopathol.035.02.1037

Matsubara H. (1998). Pathophysiological role of angiotensin II type 2 receptor in cardiovascular and renal diseases. *Circulation research*, *83*(12), 1182–1191. https://doi.org/10.1161/01.res.83.12.1182

Mierziak, J., Kostyn, K., & Kulma, A. (2014). Flavonoids as important molecules of plant interactions with the environment. *Molecules (Basel, Switzerland)*, *19*(10), 16240–16265. https://doi.org/10.3390/molecules191016240

Miura, S., Karnik, S. S., & Saku, K. (2011). Review: angiotensin II type 1 receptor blockers: class effects versus molecular effects. *Journal of the renin-angiotensin-aldosterone system: JRAAS*, *12*(1), 1–7. https://doi.org/10.1177/1470320310370852

Mitkova, Z., Dimova, A., Petrova, G., & Dimitrova, M. (2024). Adverse Drug Reactions of Cardiovascular Classes of Medicines-Data for Bulgarian Population. *Biomedicines*, *12*(10), 2163. https://doi.org/10.3390/biomedicines12102163

Raddaoui, Y., Ben Amara, A., Noamen, A., Antit, S., Hajri, Y., Habli, J., Ibn Hadj Amor, H., Ben Youssef, Y., Zakhama, L., & Fehri, W. (2024). Role of depression in blood pressure control. A cross-sectional multicentric study. *La Tunisie medicale*, *102*(1), 7–12. https://doi.org/10.62438/tunismed.v102i1.4723

Prasanth, D. S. N. B. K., Murahari, M., Chandramohan, V., Panda, S. P., Atmakuri, L. R., & Guntupalli, C. (2021). *In silico* identification of potential inhibitors from *Cinnamon* against main protease and spike glycoprotein of SARS CoV-2. *Journal of biomolecular structure & dynamics*, *39*(13), 4618–4632. https://doi.org/10.1080/07391102.2020.1779129

Putra, W. E., Sustiprijatno, Arief, H., Widiastuti, D., Heikal, M. F. (2024). Computational Screening of Rheum palmatum Phytochemicals as Potential Anti- Diabetes Agent via Sodium-Glucose Transport Protein 2 Inhibition. *Science & Technology Asia*. 29(03):256-268.

Shaito, A., Thuan, D. T. B., Phu, H. T., Nguyen, T. H. D., Hasan, H., Halabi, S., Abdelhady, S., Nasrallah, G. K., Eid, A. H., & Pintus, G. (2020). Herbal Medicine for Cardiovascular Diseases: Efficacy, Mechanisms, and Safety. *Frontiers in pharmacology*, *11*, 422. https://doi.org/10.3389/fphar.2020.00422

Sri Prakash, S. R., Kamalnath, S. M., Antonisamy, A. J., Marimuthu, S., & Malayandi, S. (2023). *In Silico* Molecular Docking of Phytochemicals for Type 2 Diabetes Mellitus Therapy: A Network Pharmacology Approach. *International journal of molecular and cellular medicine*, *12*(4), 372–387. https://doi.org/10.22088/IJMCM.BUMS.12.4.372

Sumitha, A., Devi, P. B., Hari, S., & Dhanasekaran, R. (2020). COVID-19—In silico structure prediction and molecular docking studies with doxycycline and quinine. *Biomedicine and Pharmacology Journal, 13*(3). https://dx.doi.org/10.13005/bpj/1986

Tithi, T. I., Tahsin, M. R., Anjum, J., Zaman, T. S., Aktar, F., Bahar, N. B., Tasnim, S., Sultana, A., Jahan, I., Afrin, S. S., Akter, T., Sen, P., Koly, F. J., Reza, M. S., Chowdhury, J. A., Kabir, S., Chowdhury, A. A., & Amran, M. S. (2023). An in vivo and in silico evaluation of the hepatoprotective potential of Gynura procumbens: A promising agent for combating hepatotoxicity. *PloS one*, *18*(9), e0291125. https://doi.org/10.1371/journal.pone.0291125

Uma Maheswari, K., & Sankar, S. (2024). In Silico Molecular Docking of Phytochemicals of Murraya koenigii Against Streptococcus mutans. *Cureus*, *16*(2), e53679. https://doi.org/10.7759/cureus.53679

Vardhan, S., & Sahoo, S. K. (2020). In silico ADMET and molecular docking study on searching potential inhibitors from limonoids and triterpenoids for COVID-19. *Computers in biology and medicine*, *124*, 103936. https://doi.org/10.1016/j.compbiomed.2020.103936

Ysrafil, Y., Sapiun, Z., Slamet, N. S., Mohamad, F., Hartati, H., Damiti, S. A., Alexandra, F. D., Rahman, S., Masyeni, S., Harapan, H., Mamada, S. S., Bin Emran, T., & Nainu, F. (2023). Anti-inflammatory activities of flavonoid derivates. *ADMET & DMPK*, *11*(3), 331–359. https://doi.org/10.5599/admet.1918