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Research Article

Molecular Docking of Avocado Leaf *(Persea americana)* Chemical Compounds againts Angiotensin Converting Enzyme

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ABSTRACT

Angiotensin-Converting Enzyme (ACE) plays a key role in the pathogenesis of hypertension by converting angiotensin I into the vasoconstrictive angiotensin II. Avocado leaves *(Persea americana)* are known to exhibit antihypertensive activity through ACE inhibition, comparable to that of captopril. However, the molecular interaction of compounds identified in avocado leaves with ACE has not been extensively investigated in silico. This study aimed to explore the molecular mechanisms of identified compounds in avocado leaves in inhibiting ACE through molecular docking analysis. Docking simulations were performed between the identified compounds and the ACE protein target (PDB ID: 1O86). The compounds were identified from preliminary studies and screened for potential biological activity using PASS Online. Out of 19 compounds screened, 14 showed predicted antihypertensive activity. The best docking results were observed for trans-tiliroside (ΔG –8.39 kcal/mol), quercitrin (ΔG –8.32 kcal/mol), and ficumegasoside (ΔG –8.26 kcal/mol). These three compounds demonstrated strong binding affinity towards ACE, indicating their potential as natural ACE inhibitors. The findings suggest that trans-tiliroside, quercitrin, and ficumegasoside could serve as promising candidates for the development of antihypertensive therapies derived from natural products.

Keywords: Angiotensin Converting Enzyme; antihypertension; molecular docking; *Persea americana*

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INTRODUCTION

Hypertension remains a major global health concern, including in Indonesia, with increasing incidence reported annually. According to the World Health Organization (2023), an estimated 1.28 billion adults aged 30–79 years worldwide are affected by hypertension. In Indonesia, data from the Riset Kesehatan Dasar (Riskesdas) reported a hypertension prevalence of 34.11% among individuals aged ≥18 years (Kemenkes 2018), reflecting an increase of 8.31% from the previous rate of 25.8% (Kemenkes 2013).

Hypertension, or high blood pressure, is a condition characterized by a sustained elevation of arterial pressure, which increases the workload of the heart in pumping blood throughout the body (Azizah, Hasanah, and Pakarti 2022). Individuals with hypertension typically present with blood pressure levels ≥140/90 mmHg (Soenarta et al. 2015). Current pharmacological treatments include several drug classes such as Angiotensin-Converting Enzyme inhibitors (ACEis), Angiotensin II Receptor Blockers (ARBs), Calcium Channel Blockers (CCBs), β-blockers, and diuretics (Wells et al. 2015). Although effective, these medications are often associated with adverse effects (DiPiro et al. 2020).

A study by Olowofela and Isah (2017), reported that 18.1% of 514 patients experienced side effects from antihypertensive drugs, including diuretics, CCBs, and ACEis, such as frequent urination, dizziness, headaches, and dry cough. In addition to the relatively high cost and the necessity for lifelong adherence, these side effects often lead to poor treatment compliance and have driven interest in herbal medicine as an alternative (Naqiyya 2020; Xiong et al. 2015). Medicinal plants present a promising alternative due to their minimal side effects, better biological tolerance, greater accessibility, and lower cost (Hassani, Shirani, and Hosseinzadeh 2016; Rouhi-Boroujeni et al. 2015; Wahyuni 2023). One such plant with antihypertensive potential is avocado leaves *(Persea americana),* which have been traditionally used in various communities in Indonesia. This is supported by a quasi-experimental study involving hypertensive elderly patients, which demonstrated that the administration of avocado leaf decoction significantly reduced blood pressure.

These leaves contain secondary metabolites such as flavonoids, aliphatic alkanols/acetogenins, and c-glycosyl flavones (Park et al. 2019), which have the potential to lower blood pressure. An in vivo study by Sutiningsih et al. (2022), demonstrated that avocado leaf extract significantly reduced both systolic and diastolic blood pressure in Wistar rats induced with 16% NaCl. Similarly, an in vitro study by Badejo et al. (2022), reported that methanol extract and ethyl acetate fractions of avocado leaves exhibited inhibitory activity against noradrenaline-induced contraction and ACE, comparable to that of captopril.

Based on these findings, avocado leaves hold potential as a source of active compounds for the development of antihypertensive agents targeting

Angiotensin-Converting Enzyme (ACE). However, the exact mechanism and key active compounds that interact with ACE remain unclear. Therefore, this study aims to identify the molecular mechanisms and active compounds in avocado leaves with potential ACE inhibitory activity using an in silico approach. The in silico approach is a computer-based method for evaluating the biological activity of compounds, including molecular docking techniques. Molecular docking predicts the type, position, and binding strength between active compounds (ligands) and target proteins (macromolecules) (Mirza 2019). AutoDock is widely used due to its high accuracy and validity compared to other non-commercial software (Pagadala, Syed, and Tuszynski 2017).

The active compounds from avocado leaves were obtained from the study by Park et al. (2019), and screened using PASS (Prediction of Activity Spectra for Substances) Online to assess their potential ACE inhibitory activity. The target protein used in this study is Angiotensin-Converting Enzyme (ACE), based on previous literature (Gymnastiar, Damayanti, and Tilaqza 2024; Tilaqza and Herbani 2021), and the interactions between avocado leaf compounds and ACE were analyzed using AutoDock to evaluate the binding affinity and molecular interaction mechanisms.

MATERIALS AND METHODS

Material

The test ligand compounds used in this study were obtained from previously reported phytochemical constituents of avocado leaves as described by Park et al (2019), comprising a total of 19 compounds. Activity prediction was performed using the PASS (Prediction of Activity Spectra for Substances) Online program, which was employed for activity prediction using SMILES structures to obtain the probability of activity (Pa) values (Filimonov et al. 2014). Compounds with vasoprotection and vasodilation activities with Pa > 0.5 Gymnastiar, Damayanti, and Tilaqza (2024), were selected, resulting in 14 potential compounds for further analysis.

The SMILES structures of these ligands were retrieved using their IUPAC names via the PubChem database and subsequently converted into three-dimensional structures using VegaZZ. Ligand preparation was performed using AutoDock Tools. The 3D structure of the ACE macromolecule was obtained from the Protein Data Bank (PDB) with PDB ID: 1O86. The selected structure was based on X-ray crystallography data with a resolution of 2 Å. The macromolecule originated from Homo sapiens and was already complexed with a native ligand (lisinopril).

The hardware used was an Axioo MyPC One Pro K5-24 (8N5) equipped with a 24" FHD IPS display, Intel® Core™ i5-1135G7 processor, 8GB DDR4 RAM, 512GB NVMe storage, Intel® Iris® Xe graphics, and Windows 10 Pro operating

system. The software tools utilized in this study included AutoDock for molecular docking, AutoDock Tools for ligand and macromolecule preparation, VegaZZ for 3D ligand structure optimization, and Discovery Studio Visualizer (DSV) and PyMOL for visualization and validation of docking results.

Method

Screening of Test Ligands

The PASS Online platform (https://www.way2drug.com) was used to identify potential test ligands based on the SMILES structures of active compounds obtained from the official PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The predictions generated by PASS Online are based on structural analysis of organic compounds and their potential biological activity as antihypertensive agents, represented by the Pa (Probability of Activity) value. Compound screening was performed using a Pa threshold > 0.5 for activities related to vasodilation and vasoprotection (Gymnastiar, Damayanti, and Tilaqza 2024).

Preparation of Test Ligands and Macromolecule

A total of 14 test ligands obtained from PASS Online screening were used in this study. Ligand preparation involved generating three-dimensional (3D) structures by converting SMILES retrieved from the PubChem database using VegaZZ, followed by preparation in AutoDock Tools (ADT) that included the addition of hydrogen atoms, assignment of Gasteiger partial charges, and application of Autodock force field parameters. Energy minimization was performed for 10,000 steps to obtain a stable ligand conformation with the lowest energy (Ferwadi, Gunawan, and Astuti 2017).

The 3D structure of angiotensin converting enzyme (ACE) was obtained from the Protein Data Bank (PDB ID: 1O86) with a resolution of 2 Å, which falls within the acceptable range of 1.5–3 Å for reliable molecular docking simulations (Putri et al. 2024). The structure was determined using X-ray crystallography and derived from *Homo sapiens,* providing high accuracy for macromolecular modeling (Hasan, I'annah, and Bahi 2022). This structure was selected due to the presence of a co-crystallized native ligand, lisinopril, which facilitates accurate identification of the active site.

Protein preparation was performed using ADT by removing water molecules, native ligands, and other non-essential components, followed by the addition of charges and hydrogen atoms. Water molecules were removed to prevent interference with ligan-receptor interactions and to reduce computational complexity (Sifaiya, Hasan, and Choirunniza 2024), while the native ligand was removed to avoid steric hindrance during ligand binding (Ningrat 2022). Hydrogen atoms were added because X-ray crystallographic structure typically

lack hydrogens, and their inclusion is essential to simulate physiological conditions and enable proper identification of hydrogen bonding interactions (Putri et al. 2024; Muttaqin, Ismail, and Muhammad 2019). All prepared ligands and protein structures were saved in ".pdbqt" format for subsequent molecular docking analysis.

Validation Method

Validation was performed by comparing the conformation of the native ligand in the crystal structure with the conformation of the redocked ligand into the same receptor. This procedure required defining the grid box coordinates at the known active site of the ligand-protein complex. The main validation parameter was the Root Mean Square Deviation (RMSD) value. An RMSD value ≤ 3.0 Å was considered acceptable, with three main classifications: excellent (≤ 2.0 Å), acceptable (2.0–3.0 Å), and poor (≥ 3.0 Å) (Ramírez and Caballero 2018).

Molecular Docking Process

Molecular docking simulations were conducted using AutoDock 4.0 in conjunction with AutoDock Tools based on the optimized three-dimensional structures of the ligand and target protein. Prior to docking, the grid box parameters were defined to encompass the predicted ligand-binding site and ensure adequate sampling of the interaction region. The docking protocol employed the Lamarckian Genetic Algorithm (LGA) with 100 independent runs and a population size of 150 to explore potential binding conformations. The resulting docking poses were ranked according to their predicted binding free energy (ΔG), and the most favorable complexes were further analyzed using Discovery Studio Visualizer. The interaction analysis focused on binding affinity, key amino acid residues involved in ligand binding, and the types of intermolecular interactions contributing to complex stability.

RESULTS

The selection of test ligands was based on screening results using PASS Online (Table 1).

Table 1. Screening result of compounds identified in avocado leaves using PASS Online platform for potential antihypertensive activity

Ligand	Pa Value	Activity
(6S-9R)-roseoside	0.849	Vasoprotector
Afzelin	0.963	Vasoprotector
	0.623	Vasodilator
Astragaline	0.942	Vasoprotector
	0.737	Vasodilator
Catechin	0.652	Vasoprotector
Epicatechin	0.652	Vasoprotector

Ficumegasoside	0.924	Vasoprotector
Isoorientin	0.877	Vasoprotector
	0.682	Vasodilator, coronary
Isovitexin	0.843	Vasoprotector
	0.666	Vasodilator, coronary
Juglanin	0.740	Vasodilator
	0.935	Vasoprotector
Orientin	0.682	Vasodilator, coronary
	0.884	Vasoprotector
Quercetin	0.824	Vasoprotector
Quercitrin	0.966	Vasoprotector
	0.658	Vasodilator
Trans-tiliroside	0.937	Vasoprotector
	0.711	Vasodilator
Vitexin	0.852	Vasoprotector
	0.722	Vasodilator
	0.666	Vasodilator, coronary

Note: Pa value = Probability of activity value. Compounds with Pa > 0.5 for activities related to vasodilation and vasoprotection were selected for molecular docking analysis with ACE (PDB ID: 1O86). Screening performed using PASS Online (https://www.way2drug.com).

Docking Method Validation

The purpose of docking method validation is to determine the reliability of the docking approach by comparing the crystallographic conformation of the native ligand with the conformation obtained from redocking the same ligand into the target protein using AutoDock (Hasan, I'annah, and Bahi 2022). This validation process requires the definition of the grid box coordinates at the known binding site of the protein, which serves as the active site for ligand–protein interaction.

In the validation process, it is necessary to define the grid box, which represents the center coordinates of ligand-protein interactions corresponding to the active site of the protein. The grid box center is generally determined based on the center of mass of the native ligand, while the grid box dimensions are defined according to the size of the ligand and the protein binding site containing key amino residues essential for its activity. The grid box was centered at coordinates x = 40.935, y = 32.383, and z = 47.285, with a dimension of 40 x 40 x 40 Å to adequately cover the active site region of the protein.

The Root Mean Square Deviation (RMSD) value was the primary variable observed in this validation process. The RMSD result was obtained by overlaying the interaction between the crystallographic native ligand and the redocked native ligand using PyMOL software. The validation results (the overlaying simulation) are presented in Figure 1.

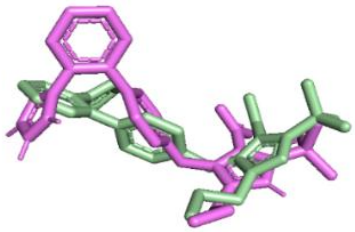

Figure 1. Overlay of the co-crystallized native ligand (lisinopril) (pale green) and the redocked native ligand (violet) in the ACE active site (PDB ID: 1O86), showing an RMSD value of 1.94 Å, indicating a valid docking protocol.

Based on the results obtained, it was identified that the redocked ligand closely approximated the position of the crystallographic ligand and occupied the same active site, as evidenced by its interaction with similar amino acid residues. The RMSD value generated for the ACE target protein was 1.94 Å, which satisfies the validity criteria, as a validation result of ≤ 2.0 Å is considered excellent according to the RMSD classification (Ramírez and Caballero 2018). These findings indicate that the docking method used is valid, and therefore, the docking procedure can be reliably performed using AutoDock.

Molecular Docking Result

Molecular docking was performed on 14 test ligands obtained from the screening process, which were docked to the target protein. The docking results were analyzed based on several parameters, including binding energy (ΔG), interacting amino acid residues, and types of molecular interactions. The ACE target protein complexed with the native ligand lisinopril showed a binding energy of –8.50 kcal/mol. Based on the binding energy values, 3 test ligands were selected from the total of 14, as they exhibited binding energies closest to that of the native ligand.

Table 2. RMSD value from docking results

No.	Test Ligand	Binding Energy (kcal/mol)
		ACE (1O86)
		-8.50
1.	(6S-9R)-roseoside	-6.51
2.	Afzelin	-8.04
3.	Astragaline	-7.56
4.	Catechin	-7.00
5.	Epicatechin	-6.90
6.	Ficumegasoside	**-8.26**
7.	Isoorientin	-6.50
8.	Isovitexin	-6.50
9.	Juglanin	-7.45
10.	Orientin	-7.30
11.	Quercetin	-6.83
12.	Quercitrin	**-8.32**
13.	Trans-tiliroside	**-8.39**
14.	Vitexin	-6.05

Based on the results presented in the table above, three selected test ligands demonstrated the strongest binding affinities to the ACE target protein: trans-tiliroside (ΔG –8.39 kcal/mol), quercitrin (ΔG –8.32 kcal/mol), and ficumegasoside (ΔG –8.26 kcal/mol). Further analysis was conducted to identify the interacting amino acid residues and types of bonds formed between each test ligand and the target protein. The results of this analysis are presented in Table 3.

Table 3. Molecular docking results of selected ligands on ACE protein (PDB ID: 1O86)

Compounds	Interacting Residues	
	Hydrogen Bond	**Non-Hydrogen Bond**
Lisinopril (native ligand)	Ala354; Tyr520	Gln369; Asp377; Val380; Glu384; Glu162; His353; Gln281; Lys511; Phe457; Tyr523; His383; His513; Phe512; Val518; Glu411; Ser355; His387; Ala356
Ficumegasoside	Glu162; Lys511; **Tyr520;** Tyr523; His513; Ala356; His353	**Gln281;** Phe457; **Glu384; Glu411; His387; His383; Ser355; Val518; Phe512;** Ala354; Leu161; Trp279; Tyr146
Quercitrin	His513; His387; Glu411; Glu384; Glu162	**Ala356; Ser355; His353;** Ala354; **Val380; His383;** Val379; Lys454; Asp415; Phe527; **Phe512; Tyr523; Val518**
Trans-tiliroside	**Ala354;** Asp415; Glu376; **Tyr520;** Glu162; His513	Gln530; **Ser355; Glu384;** Lys454; Phe527; **His383; Val380;** Asn285; Asn277; **Asp377; Gln281;** Thr166; **Lys511;** Tyr146; Leu161; Trp279; **His353; Tyr523**

Bold text: Amino acid residues shared in interaction with the native ligand.

DISCUSSION

At the molecular level, ACE consists of three main active site pockets—S, S1′, and S2′—each comprising different amino acid residues. The S site (Ala354, Glu384, Tyr523) is the primary location where the Ang I substrate is converted into Ang II and is situated between α13 and α14 helices. The S1′ site (Glu162) is involved in binding additional residues from the substrate, contributing to specificity for larger substrates. The S2′ site (Gln281, His353, Lys511, His513, Tyr520) enhances interactions with more complex substrates. The zinc-binding motif (HEXXH), considered a key catalytic site, includes residues His383, Glu384, His387, and a zinc ion (Heo et al. 2023; Masuyer et al. 2012; Natesh et al. 2003).

In the present study, the initial screening of compounds can be explained through their relevance to the renin–angiotensin–aldosterone system (RAAS), particularly involving the angiotensin-converting enzyme (ACE), which converts angiotensin I into the vasoconstrictor angiotensin II. This peptide increases vascular resistance, promotes aldosterone-mediated fluid retention, and reduces nitric oxide (NO) bioavailability, leading to endothelial dysfunction and elevated blood pressure (Karlina et al. 2021). In this context, vasodilatory and vasoprotective activities, although not directly equivalent to ACE inhibition, are functionally relevant as they counteract the downstream effects of angiotensin II

(Ma and Chen 2022; Ranadive et al. 2021; Mas-Capdevila et al. 2019). Therefore, compounds exhibiting these properties may contribute to antihypertensive effects associated with RAAS dysregulation without directly indicating ACE inhibition.

Based on the results, the three selected test ligands exhibited molecular interactions with several key amino acid residues similar to those of the native ligand, forming various types of bonds. Trans-tiliroside, which showed the highest binding affinity with a ΔG value of –8.39 kcal/mol, formed hydrogen bonds with Ala354, Asp415, Glu376, Tyr520, Glu162, and His513—two of which (Ala354 and Tyr520) were identical to those involved in the native ligand interaction. This indicates a stable ligand–receptor complex (Setyawati, Santika, and Yustiantara 2022). Hydrogen bonds are essential in determining the binding affinity of ligand–receptor interactions; ligands forming more hydrogen bonds are generally more strongly and easily bound to the receptor's active site (Irsal et al. 2022). Trans-tiliroside was shown to interact extensively with the main active site pocket, suggesting its potential as a competitive ACE inhibitor by occupying the substrate-binding site.

Previous studies have demonstrated that tiliroside exerts antihypertensive and vasorelaxant effects, including blood pressure in hypertensive animal models, likely through inhibition of vascular L-type calcium channels and reduction of peripheral resistance. In addition, tiliroside and trans-tiliroside exhibit antioxidant and anti-inflammatory activities, which may contribute indirectly to cardiovascular protection by mitigating oxidative stress and endothelial dysfunction, two key mechanisms implicated in hypertension pathophysiology (G. C. Silva et al. 2013; Qiao et al. 2011; B. R. Silva, Pernomian, and Bendhack 2012).

The second compound, quercitrin, exhibited a binding energy of ΔG –8.32 kcal/mol and formed hydrogen bonds with residues His513, His387, Glu411, Glu384, and Glu162. This interaction pattern differs from that of the native ligand, indicating a unique binding mechanism to ACE. Quercitrin interacts with the zinc-binding motif (HEXXH), specifically through hydrogen bonds with His387 and Glu411, and non-hydrogen bonding with His383. The residues His387, His383, and Glu411 constitute the HEXXH motif, where His383 and His387 serve as the two key histidine residues coordinating the zinc ion on helix α13, while Glu411, located on helix α14, functions as an auxiliary ligand via acetate coordination. The zinc ion plays a critical role in ACE's catalytic mechanism, which resembles that of thermolysin, as both are zinc metalloproteases responsible for peptide bond hydrolysis (Natesh et al. 2003). Therefore, quercitrin may inhibit ACE by interfering with its catalytic mechanism through direct interaction with the zinc-binding motif. Quercitrin, as a glycosylated derivative of quercetin (Tang et al. 2019), may contribute to antihypertensive effects through mechanisms associated with quercetin, including antioxidant activity, vasodilation, and modulation of the renin-angiotensin system. Previous studies on quercetin have shown inhibition of ACE activity in experimental and in silico models, supporting the plausibility of a

blood pressure-lowering role for quercitrin (Parichatikanond, Pinthong, and Mangmool 2012).

The third test ligand, ficumegasoside, demonstrated the third-highest binding energy (ΔG –8.26 kcal/mol). This value is close to that of the native ligand, suggesting a relatively stable interaction. Ficumegasoside interacts with several amino acid residues shared with the native ligand, including Tyr520, Gln281, Glu384, Glu411, His387, His383, Ser355, Val518, and Phe512. These interactions involve van der Waals forces, hydrophobic interactions, and hydrogen bonds. The compound interacts with residues within the primary active site pocket of ACE, including Tyr520 and Gln281 at the S2′ pocket, Glu384 at the S pocket Heo et al. (2023), and the HEXXH zinc-binding motif (His387 and His383) coordinated to the zinc ion on helix α13, along with Glu411 on helix α14 serving as an additional catalytic ligand via acetate (Natesh et al. 2003).

Ficumegasoside has been identified as a megastigmane glycoside isolated from the leaves of *Ficus microcarpa* (Phan et al. 2011), although specific evidence for ficumegasoside remains limited, related glycosidic constituents and megastigmane glycoside have been associated with cardiovascular activities, including antihypertensive, vasorelaxant, and antioxidant effects. This suggests that ficumegasoside may contribute to antihypertensive activity through multiple mechanisms (Yan et al. 2017).

The drug potential of these compounds should be evaluated based on their natural availability and physicochemical properties. Trans-tiliroside and quercitrin are flavonoid glycosides (Luhata and Luhata 2017; Septembre-Malaterre et al. 2022), while ficumegasoside is a megastigmane glycoside Phan et al. (2011), all of which are plant-derived and relatively accessible. However, their high polarity and molecular weight may limit membrane permeability and oral bioavailability, although glycosylation can improve solubility and stability (Rampadarath et al. 2022). Therefore, despite promising in silico results, further pharmacokinetic (ADME) studies and optimization strategies are required to enhance their drug-likeness and therapeutic potential.

CONCLUSIONS

Trans-tiliroside, quercitrin, and ficumegasoside demonstrated promising binding interactions with key active and catalytic residues of angiotensin-converting-enzyme (ACE), indicating their potential as antihypertensive agents. Trans-tiliroside showed the highest binding affinity and interaction within the main active site, while quercitrin and ficumegasoside exhibited distinct binding modes involving the zinc-binding motif and catalytic regions. These findings suggest that plant-derived glycosides may exert antihypertensive effect through ACE inhibition and related mechanisms. However, their physicochemical limitations highlight the need for further pharmacokinetic evaluation and experimental validation.

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