IBJ
Indonesian Biodiversity Journal
http://ejurnal.unima.ac.id/index.php/ibj

indonesian.biodivers.j.
Vol. 6, No. 3, December 2025
ISSN : 2722-2659

COMPARATIVE IN SILICO STUDY OF SIX FLAVONOID COMPOUNDS AS ACE INHIBITORS USING MOLECULAR DOCKING METHOD

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Received: December 10th, 2025 *Accepted: May 5th, 2026*

Abstract

Hypertension, also known as high blood pressure, is a condition characterized by increased blood pressure in the arteries. Flavonoids are secondary metabolites that can be used as antihypertensives. One of the target proteins in the body associated with hypertension is Angiotensin Converting Enzyme (ACE). This study aims to predict the ACE-inhibitory activity, physicochemical properties, and toxicity of flavonoid compounds, including catechin, kaempferol, luteolin, apigenin, quercetin, and naringenin. Physicochemical predictions were performed using the SwissADME website, with Lipinski's five rule parameters. The six flavonoid compounds met the parameters. Toxicity predictions were performed using the pkCSM online tool, which considers three parameters: Ames toxicity, hepatotoxicity and hERG inhibition. The six test compounds and the reference ligand, captopril, showed negative results across all three parameters. Compound activity was predicted computationally using molecular docking. The results showed that the test compound, quercetin, produced the highest rank score, indicating the best activity prediction among the six test compounds, and it works suggests a similar binding mode to ACE inhibitors. Catechin, kaempferol, luteolin, apigenin, and naringenin are recommended for further research as antihypertensive drug candidates.

Keywords: Angiotensin Converting Enzyme, Flavonoids, Hypertension, Molecular Docking

INTRODUCTION

In 2024, the number of adults aged ≥30 years with hypertension reached 1.4 billion, equivalent to 33% of the population in that age range, with ⅔ living in low- and middle-income countries, including Indonesia (Siregar et al., 2021). Many sufferers experience hypertension without knowing the condition; this reason makes it known as the silent killer, with cases often occurring among many sufferers who feel healthy and do not show symptoms even though their blood pressure is high (Gustam et al., 2024). On the other hand, 630 million sufferers have been diagnosed and received treatment. Still, only half have achieved blood pressure control in line with clinical targets (WHO, 2025).

The estimated number of people with hypertension in Indonesia is 63,309,620 (Kemenkes RI, 2018). Furthermore, hypertension is a significant contributing factor to stroke, the second leading cause of death worldwide (Goorani et al., 2025; Feigin et al., 2024; Yang et al., 2017). Other complications include kidney failure, coronary heart disease, and blindness (Lakoro et al., 2023). In addition to impacting health, hypertension also has a significant economic burden. Research has found that treatment and

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ISSN : 2722-2659

management of hypertension complications constitute a considerable expense in the health sector, especially for developing countries (Suantika et al., 2025).

Hypertension is a medical condition characterized by abnormally and continuously elevated blood pressure in the arteries, with systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg (Iqbal & Jamal, 2023). The main factor that caused this condition is impaired heart function in maintaining normal blood pressure (Wulandari et al., 2023). Most current hypertension management guidelines recommend therapy with angiotensin-converting enzyme inhibitors (ACEIs) (Xu et al., 2015). The discovery of ACEIs was a significant advancement in the treatment of hypertension (Widiasari, 2018). ACE inhibitors inhibit the conversion of angiotensin I to angiotensin II by blocking ACE activity, thus controlling hypertension. (Zheng et al., 2022), And one drug with this mechanism is captopril (Marte et al., 2024). Captopril is a first-line medication for hypertension, but its use can cause several side effects that can potentially reduce patient compliance. These side effects include dry cough, proteinuria, and renal insufficiency. ACE inhibitors can also cause hyperkalemia; this is especially dangerous because it can lead to fatal arrhythmias (Marte et al., 2024).

The use of traditional medicine is generally considered safer than modern medicine because it has relatively fewer side effects (Widiasari, 2018). Flavonoids are categorized as secondary metabolites that can be used as antihypertensives (Andika et al., 2020). Flavonoid compounds are polar compounds because the -OH group forms hydrogen bonds (Satria et al., 2022). Flavonoid derivatives include kaempferol, luteolin, apigenin, catechins (Mardiyah et al., 2025), quercetin, and naringenin (Widiasari, 2018). Kaempferol is one of the most commonly found flavonoid aglycones, usually in the form of glycosides. Kaempferol has a molecular formula of $C_{15}H_{10}O_6$ (Figure 1A) (Imran et al., 2019). Luteolin (3′,4′,5,7-tetrahydroxy flavone) is a phytochemical that belongs to the flavonoid class (Figure 1B) (Aziz et al., 2018). Apigenin (4′,5,7-trihydroxyflavone, $C_{15}H_{10}O_5$) is categorized as a flavonoid. The structure of apigenin (Figure 1C) is a compound with a molecular mass of 270.23 g/mol and a melting point ranging from 345-350°C. This compound acts as a vasodilator (vasorelaxant) and has antihypertensive activity (Yulianto et al., 2017).

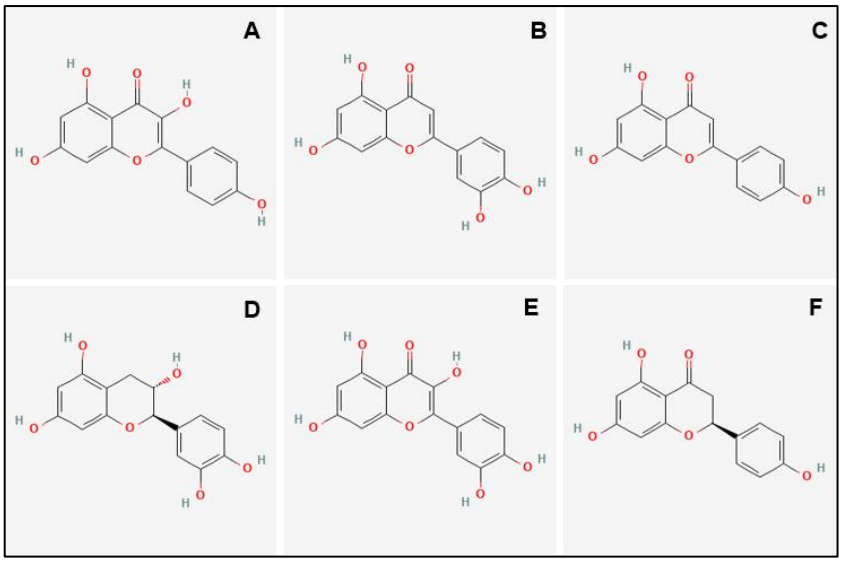


Figure 1. Visualization of the molecular docking results of the flavonoid test compound with the Angiotensin Converting Enzyme (4CA5) receptor in 2D form (A. Kaempferol, B. Luteolin, C. Apigenin, D. Catechin, E. Quercetin, and F. Naringenin) https://pubchem.ncbi.nlm.nih.gov/ .

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Catechin is a flavonoid with 15 carbon atoms arranged in a C_6–C_3–C_6 pattern (Wang et al., 2018). Catechin has a molecular formula of $C_{15}H_{14}O_6$ (Figure 1D) (Mahendra & Azhar, 2022). One candidate natural compound that can be used as an alternative therapy for hypertension is quercetin (Figure 1E). This compound is known to have pharmacological effects in lowering blood pressure through the mechanism of inhibiting the ACE (Utari et al., 2021). Naringenin is included as a flavonoid compound. The molecular weight of Naringenin ($C_{15}H_{12}O_5$) is 272.26. Chemically, Naringenin's structure is 2,3-dihydro-5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-on. Naringenin is a flavanone class of flavonoids (Figure 1F) (Ardiana et al., 2022).

In silico testing is performed using molecular docking to predict its activity on specific target cells. The process of aligning a ligand, a small molecule, with a target cell, a large protein molecule, is known as docking. The binding energy value generated through in silico testing is also known as the binding free energy (ΔG). Bonding between a ligand and a receptor requires a binding energy, which indicates the amount of energy. A lower binding energy indicates greater stability of the bond with the receptor, and its activity can be predicted to be greater (Astuti et al., 2021).

Based on previous research on the side effects of first-line drugs, namely captopril in antihypertensive therapy, and research on flavonoid compounds that can be used in antihypertensive therapy with relatively minor side effects, the use of flavonoid compounds can be an alternative antihypertensive therapy by minimizing the side effects of using synthetic drugs such as captopril. The in silico approach is an effective and efficient initial stage in evaluating the affinity and interaction mechanism of flavonoid amino acids to antihypertensive target proteins. It can indicate the most potent compound candidates for further studies, both in vitro and in vivo.

RESEARCH METHODS

Tools and Materials

The hardware used in this study was an ASUS Vivobook Go 14/15 laptop running Windows 11 Home Single Language, with an Intel(R) Core(TM) i3-N305 1.80 GHz processor, 8.00 GB RAM, and an internet connection. The software used in this study includes Autodock Tools 1.5.7, Open Babel, BIOVIA Discovery Studio 2017, Avogadro, Notepad, the GNINA site, the Protein Data Bank (PDB) site, the PubChem site, the pkCSM pharmacokinetics site, and the SwissADME site.

The three-dimensional structure of Angiotensin Converting Enzyme was downloaded from the Protein Data Bank (PDB) via the Research Collaboratory for Structural Bioinformatics (RCSB) website (https://www.rcsb.org/). The selected macromolecule is Human Angiotensin Converting Enzyme in complex with the phosphinic tripeptide FI, determined by X-ray diffraction at 1.85 Å resolution. The PDB ID of the macromolecule is 4CA5 in (.pdb) format. The ligand structure used is the native ligand of 4CA5, namely 3EF1700, the reference compound captopril, and six flavonoid compounds, then downloaded from https://pubchem.ncbi.nlm.nih.gov/in (.sdf) format.

Prediction of Physicochemical Properties

Prediction of the physicochemical properties of compounds begins by entering the canonical SMILES format of the test compound based on information from the Pubchem database into the SwissADME website https://www.swissadme.ch/ (Hess et al., 2024). Lipinski's five laws are a reference set of physicochemical properties for a compound, including the logarithm of the partition coefficient (Log P), molecular weight (MW), Hydrogen Bond Donors (HBD), and Hydrogen Bond Acceptors (HBA) (Dewi et al., 2023).

Optimization of Test Compounds

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ISSN : 2722-2659

The compounds analyzed were flavonoids, including kaempferol, luteolin, apigenin, catechin, quercetin, and naringenin. The 3D conformation reference ligand captopril was downloaded from the PubChem website in .sdf format (Putri et al., 2024). Energy minimization using Avogadro software for the test compounds and reference ligands with MMFF94 (Molecular Mechanics Force Field) parameters. Optimization aims to obtain a stable ligand conformation with the lowest energy (Mohanty & Mohanty, 2023). The test compounds and reference ligands are stored in .pdb format (Prasetio et al., 2021).

Native Protein-Ligand Preparation

The preparation of the Angiotensin Converting Enzyme protein-ligand with the PDB ID code 4CA5, downloaded from the Protein Data Bank website, will initially be carried out by removing water molecules using BIOVIA Discovery Studio software, because, in general, protein structures in the PDB still contain water molecules (H_2O), and other residues. Removing water molecules prevents interference during docking simulations and ensures the actual interaction is between the ligand and the receptor. Then, the protein chain, namely chain A, is separated from the native ligand 3EF1700 using BIOVIA Discovery Studio software. If the receptor and native ligand are completely clean, then both are saved as .pdb format (Prasetio et al., 2021).

Kollman charges and polar hydrogens were added to the receptor, along with Gasteiger charges and hydrogens. Then, non-polar charges were merged, and the native ligand's active torque was adjusted using AutodockTools. The purpose of adding these hydrogen atoms was to change the docking conditions to approach pH 7 (Hakiki et al., 2024). The native receptor and ligand were saved in .pdbqt format (Prasetio et al., 2021).

Preparation of Test Compounds

The test compound and captopril reference ligand were prepared by adding Gasteiger Charges and Hydrogen, then merging non-polar and adjusting the active torque on the ligand using AutodockTools software. The test compound and reference ligand were saved in .pdbqt format (Prasetio et al., 2021).

Docking Method Validation

The native ligand is redocked onto the target protein using the GNINA site. Previously, a grid box was created to obtain the coordinates of the native ligand, which will be used as the coordinates for the test and reference ligands using AutodockTools software (Nugroho & Fauzi, 2024). The redocking process between the protein and the native ligand is performed using the rigid method. This validation process begins with setting the grid box in the form of the size and coordinates of the point on the active site of the protein with a size of 55x55x55 Å, a space of 0.375 Å, and the following coordinates x=13.563, y=-6.087, z=20.818 (Hakiki et al., 2024). The validation result parameter is the Root Mean Square Deviation (RMSD) value. The test is declared valid when the RMSD result is ≤ 2 Å (Puratchikody et al., 2016).

Molecular Docking of Test Ligands Against Proteins

The molecular docking process begins by converting the receptor, default ligand, test ligand, and reference ligand files from .pdbqt format to .pdb format using Open Babel, then uploading and preparing them to the GNINA site with a predetermined grid box size (McNutt et al., 2021). This process produces a binding free energy (ΔG) value for the test ligand and the target receptor, and the most negative ΔG value is selected as the best result (Montolalu et al., 2025).

Interaction Analysis and Visualization

Data analysis was performed based on the binding free energy results generated from the molecular docking. The binding free energy value indicates the strength of the bond between the ligand and the

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receptor. The lower the binding free energy value, the stronger the bond between the ligand and the receptor. Interaction visualization was then performed using BIOVIA Discovery Studio software to observe the interactions formed (Putri et al., 2024).

ADMET Prediction

In the process of discovering new drugs, not only is the strength of ligand binding to the target protein assessed, but also pharmacokinetics and toxicity are evaluated to determine the drug's effectiveness and therapeutic potential. The pharmacokinetic process, or the drug's journey through the body, begins with absorption, distribution, metabolism, excretion, and toxicity. One site for predicting pharmacokinetic properties is pkCSM (https://biosig.lab.uq.edu.au/pkcsm/; Hakiki et al., 2024).

RESULTS AND DISCUSSION

Prediction of Physicochemical Properties

One step in in silico research is to determine the physicochemical properties of candidate oral drug compounds using Lipinski's Rule of Five (Hartati et al., 2021). The parameters used in Lipinski are a molecular weight of no more than 500 Daltons, a hydrogen donor of no more than 5, a hydrogen acceptor of no more than 10, a Log P of no more than 5, and a molar refraction of 40-130. Lipinski stated that orally active drugs must not violate more than one of the Lipinski's Rule of Five criteria (Kelutur et al., 2020). Molecular weight affects a compound's ability to diffuse through cell membranes by passive diffusion. If the molecular weight of a compound is >500 g/mol, the compound's ability to penetrate the cell membrane becomes increasingly complex (Shofi, 2021). Topology Polar Surface Area (TPSA) is used to assess a drug's ability to enter cells (Abdullah et al., 2021). The TPSA value for drugs with good bioavailability is in the range of 20-130 Å (Putra et al., 2020).

The molar size of a chemical molecule is then determined using Molar Refraction (MR). The calculation of molar refraction is represented by the Calculated Molar Refraction (CMR) value. Molar refraction is a steric property of a molecule that can influence how a drug interacts with a receptor (Hakiki et al., 2024). The molar refractivity range is 62.17 to 131.57 cm³/mol (Abdullah et al., 2021). Furthermore, hydrogen bond donors are OH and NH groups, and hydrogen bond acceptors are O and N atoms. The number of hydrogen bond donors and acceptors affects a compound's biological activity. The number of hydrogen bond donors and acceptors in the ligand can determine its flexibility and binding affinity for the target protein or enzyme. The value parameter of Hydrogen Bond Donors (HBD) is ≤5, and the value of Hydrogen Bond Acceptors (HBA) is ≤10 (Dewi et al., 2023). Then, log P describes a compound's ability to dissolve in non-polar solvents, such as lipids, fats, and oils (Hakiki et al., 2024).

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

Compound Name	MW (g/mol)	HBD	HBA	Log P	MR (cm^3 /mol)	TPSA (Å²)	Lipinski
Kaempferol	286.24	4	6	2.28	76.01	111.13	Fulfil
Luteolin	286.24	4	6	2.28	76.01	111.13	Fulfil
Apigenin	270.24	3	5	2.58	73.99	90.90	Fulfil
Catechin	290.27	5	6	1.22	74.33	110.38	Fulfil
Quercetin	302.24	5	7	1.99	78.03	131.36	Fulfil
Naringenin	302.24	3	5	2.19	71.57	86.99	Fulfil
Captopril	217.29	1	3	0.25	59.97	96.41	Fulfil

MW: Molecular Weight; HBD: Hydrogen Bond Donors; HBA: Hydrogen Bond Acceptors; MR: Molar Refraction; TPSA: Topology Polar Surface Area

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Based on the test results of all Lipinski's Rule of Five rules, as seen in Table 1, the reference compound captopril and six flavonoid compounds and their derivatives, as seen from the measured parameters (molecular weight, log P value, donor hydrogen bond, acceptor hydrogen bond, and molar refraction) have met the requirements to proceed to the molecular docking process. Although one test compound, quercetin exceeds the recommended TPSA for optimal oral bioavailability, but does not violate Lipinski's Rule of Five and the reference compound captopril does not meet the molar refraction criteria, it still meets the RO5 criteria because there is only one violation, and it will continue to the docking process (Hakiki et al., 2024).

Docking Method Validation

Method validation is performed to determine whether the parameter values used meet the requirements for its use, ensuring acceptable analysis results. The sizes of the native ligand and test compound are adjusted to the grid box size, whose coordinates (x, y, and z dimensions) have been set, including the grid center and grid size. Thus, the native ligand can only interact with the target protein at its designated binding site (Utari et al., 2021).

The RMSD value describes the deviation from the expected docking results. A smaller RMSD value indicates a minor deviation in docking errors (Frimayanti et al., 2021). Based on receptor validation with native ligands, the RMSD for Angiotensin Converting Enzyme (4CA5) was 0.91 Å, indicating that the receptor met the validation criteria (Dewi et al., 2023).

Ligand-Receptor Molecular Docking Results

After obtaining the protein, ligand, and active site, docking simulations were performed. The docking simulation results revealed that six flavonoid compounds had affinity: apigenin, quercetin, luteolin, kaempferol, catechin, and naringenin. These six compounds were then evaluated for their binding energy or affinity, and amino acid interactions using the GNAINA website and BIOVIA Discovery Studio 2017 software (Putri et al., 2024).

Gibbs free energy (ΔG) and inhibition constant (Ki) data can be used to analyze docking results. The affinity between the test compound and the receptor is indicated by the binding energy. The more stable the bond between the protein and the resulting ligand, the lower the binding energy value (Manna et al., 2017). Possible bonds, such as hydrogen, van der Waals, and hydrophobic bonds, are also considered parameters to help determine the relationship between structure and activity (Frimayanti et al., 2021). The inhibition constant value indicates the resistance to ligand-receptor interaction. A lower Ki indicates stronger ligand–receptor affinity, thereby increasing the ligand's affinity for the receptor (Muttaqin et al., 2019).

This study used six flavonoid ligands docked to the Angiotensin Converting Enzyme receptor, each producing nine conformations ranked by the best binding energy (Putri et al., 2024). The molecular docking results are shown in Table 2. The free binding energy (ΔG) results of the native ligand are -11.58290 kcal/mol, and Captopril is -5.82396 kcal/mol. Among the flavonoid test compounds, all show good free binding energy values. The best value is found in the Quercetin compound at -10.04800 kcal/mol, followed by Luteolin at -9.85560 kcal/mol, Kaempferol at -9.63338 kcal/mol, Apigenin at -9.59156 kcal/mol, Catechin at -9.57846 kcal/mol, and Naringenin at -9.28216 kcal/mol. These results indicate that the flavonoid test compound has potent inhibitory activity against Angiotensin Converting Enzyme, as its ΔG value is close to that of the native ligand (Hakiki et al., 2024).

Based on the inhibition constant (Ki) value, the smaller the inhibition constant, the greater the inhibition strength. The results of the inhibition constant of the native ligand are 3.23 nM (nanomolar) and the reference compound Captopril 53.8 μM (micromolar), for 6 test compounds, namely, Quercetin 43.1

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nM, Luteolin 59.7 nM, Kaempferol 89.4 nM, Apigenin 93.2 nM, Catechin 95.3 nM, Naringenin 157 nM (Hakiki et al., 2024). These results indicate that Quercetin has the best affinity among the five test compounds, as it has the lowest binding energy and inhibition constant (Putri et al., 2024).

Based on Table 2, of the six test ligands and the native ligand, only Naringenin does not share any amino acid residues with the reference ligand, Captopril. The test ligand that showed the highest number of amino acid residue matches with the reference ligand, Captopril, is Catechin (6 amino acid residues), followed by Luteolin (5 amino acid residues), Apigenin and Quercetin (4 amino acid residues), and Kaempferol (3 amino acid residues). Meanwhile, the native ligand only had one amino acid residue match. However, hydrogen bonds formed only between the test ligands Luteolin and Catechin, with a single bond. The greater number of hydrogen bonds formed is predicted to increase the ligand's activity as an ACE inhibitor (Frimayanti et al., 2021). However, binding affinity is not solely determined by the number of hydrogen bonds.

Visualization of the results of molecular docking of the flavonoid Kaempferol test compound with the Angiotensin Converting Enzyme (4CA5) receptor in 2D form, in the flavonoid Kaempferol test compound the amino acid residues that work on the active side are in the van der Waals bond PHE A:359, TYR A:360, TRP A:59, GLU A:123, THR A:92, ARG A:124, ASN A:85, ANS A:136, ALA A:189, LEU A:132, and hydrogen bonds work on the active side ASP A:358, for Alkyl (Pi-Alkyl) interactions work on ALA A:63, for Pi-Sigma interactions work on ILE A:88 and for Pi-Pi T-shaped interactions work on TYR A:62.

Table 2. Docking Results of Test Compounds and Reference Ligands

	Parameter					
Ligand Name	Free Energy of Bonding (kcal/mol)	Inhibition Constant	Amino Acid Compatibility with Captopril	Hydrogen Bonds	Van der Waals Bond	Others
Captopril	-5.82396	53.8 µM	-	TRP A: 59	ARG A:124, GLU A:123, ALA A:125, ALA A:89, ILE A:88, TYR A:360, TYR A:62	TRP A: 59 THR A:92
Kaempferol	-9.63338	89.4 nM	TYR A:360, GLU A:123, ARG A:124	ASP A:358	PHE A:359, TYR A:360, TRP A:59, GLU A:123, THR A:92, ARG A:124, ASN A:85, ANS A:136, ALA A:189, LEU A:132	ALA A:63 TYR A:62 ILE A:88
Luteolin	-9.85560	59.7 nM	TRP A:59, GLU A:123, TYR A:62 ALA A:63 ILE A:88	ASP A:358, TRP A:59, THR A:92, ARG A:124	PHE A:359, GLU A:123	TYR A:62 TYR A:360 ALA A:63 ILE A:88
Apigenin	-9,59156	93.2 nM	TYR A:360, GLU A:123, ARG A:124, ALA A:89,	ASP A:358	PHE A:359, TYR A:360, TRP A:59, THR A:92, GLU A:123, ARG A:124, ALA A:89, LEU A:132, ASN A:85, ASN A:136	TYR A:62 ALA A:63 ILE A:88
Catechin	-9.57846	95.3 nM	TRP A: 59 GLU A:123, ALA A:89, ALA A:125, ARG A:124, TYR A:360	ASN A:85, TRP A:59	THR A:92, GLU A:123, ALA A:89, ALA A:125, LEU A:122, ASN A:136, ARG A:124, ASP A:358, TYR A:360	ILE A:88 TYR A:62 ALA A:63
Quercetin	-10.04800	43.1 nM	TYR A:360, GLU A:123, ARG A:124, ALA A:89,	-	ASP A:358, TYR A:360, TRP A:59, ASN A:66, THR A:92, GLU A:123, ARG A:124, ALA A:89, LEU A:132, ASN A:85, ASN A:136	TYR A:62 ALA A:63 ILE A:88

Naringenin	-9.28216	157 nM	-	GLU A:143, HIS A:513, TYR A:523, GLU A:411, SER A:355	TRP A:357, ASN A:70, VAL A:351, ALA A:356, PHE A:391, HIS A:387, ZN A:1001, ARG A:522, VAL A:518, HIS A:353, SER A:516	PHE A:512
Native Ligand	-11.58290	3.23 nM	TYR A:360	ALA A:356, TYR A:523, HIS A:513, HIS A:353, TYR A:520, GLN A:281, LYS A:511	HIS A:410, SER A:355, GLU A:384, PHE A:512, ARG A:522, ALA A:354, ZN A:1001, TYR A:360, PHE A:457, ASP A:415, LYS A:454, THR A:282, VAL A:379, GLU A:376	VAL A:380 HIS A:383 PHE A:527 HIS A:387 PHE A:391 VAL A:518 GLU A:411

Visualization of molecular docking results of flavonoid test compound Luteolin with Angiotensin Converting Enzyme (4CA5) receptor in 2D form, in the flavonoid test compound Apigenin amino acid residues that work on the active side are in the van der Waals bond PHE A:359, GLU A:123, and hydrogen bonds work on the active side ASP A:358, TRP A:59, THR A:92, ARG A:124, for Alkyl (Pi-Alkyl) interactions work on ALA A:63, in Pi-Sigma interactions work on ILE A:88 and for Pi-Pi T-shaped interactions work on TYR A:62 and TYR A:360. The interaction of amino residues of the luteolin test compound forms unfavorable donor-donor bonds on ARG A:124 involving atoms in the test compound whose bonds repel each other with atoms in amino acids (Reynaldi et al., 2023). Unfavorable donor-donor bonds can affect the stability of drug activity. The formation of unfavorable interactions in protein-ligand complexes can reduce the complex's stability due to repulsive forces (Maulida et al., 2025).

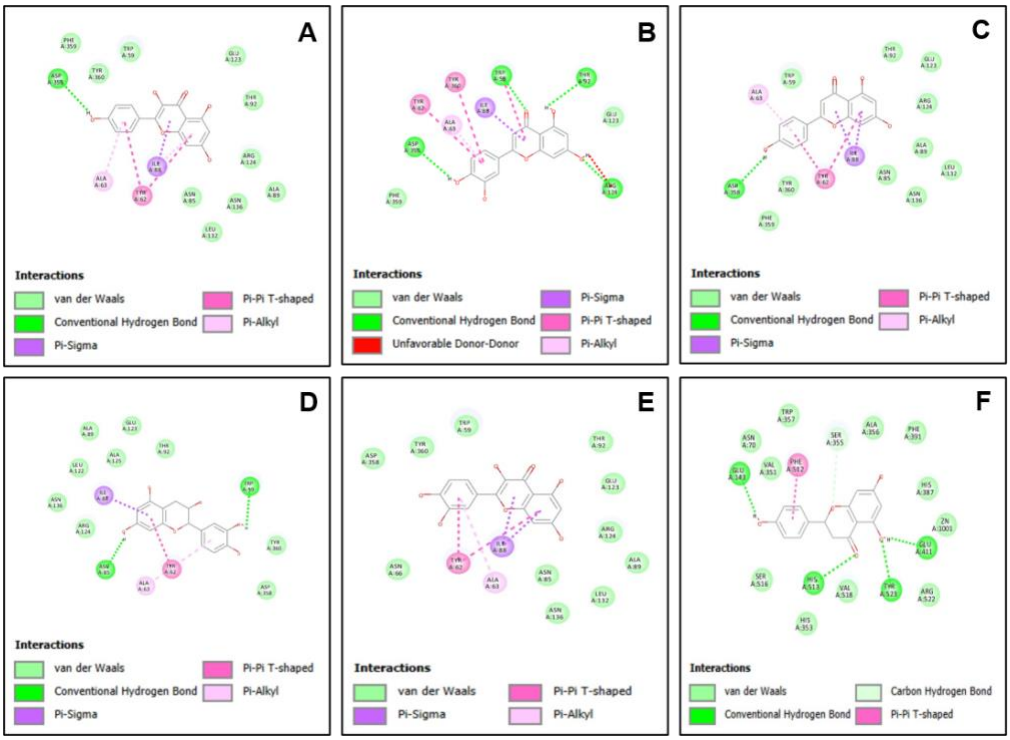


Figure 2. Visualization of the molecular docking results of the flavonoid test compound with the Angiotensin Converting Enzyme (4CA5) receptor in 2D form (A. Kaempferol, B. Luteolin, C. Apigenin, D. Catechin, E. Quercetin, and F. Naringenin).

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ISSN : 2722-2659

Visualization of molecular docking results of the flavonoid test compound Apigeninwith the Angiotensin Converting Enzyme (4CA5) receptor in 2D form, in the flavonoid Apigenin test compound, the amino acid residues that work on the active side are the van der Waals bonds PHE A:359, TYR A:360, TRP A:59, THR A:92, GLU A:123, ARG A:124, ALA A:89, LEU A:132, ASN A:85, ASN A:136, and hydrogen bonds work on the active side ASP A:358, for Alkyl (Pi-Alkyl) interactions work on ALA A:63, for Pi-Sigma interactions work on ILE A:88 and for Pi-Pi T-shaped interactions work on TYR A:62.

Visualization of molecular docking results of the flavonoid Catechin test compoundwith the Angiotensin Converting Enzyme (4CA5) receptor in 2D form, in the flavonoid Apigenin test compound the amino acid residues that work on the active side are in the van der Waals bond THR A:92, GLU A:123, ALA A:89, ALA A:125, LEU A:122, ASN A:136, ARG A:124, ASP A:358, TYR A:360, and hydrogen bonds work on the active side ASN A:85, TRP A:59, for Alkyl (Pi-Alkyl) interactions work on ALA A:63, in Pi-Sigma interactions work on ILE A:88 and for Pi-Pi T-shaped interactions work on TYR A:62.

Visualization of the results of molecular docking of the flavonoid Quercetin test compound with the Angiotensin Converting Enzyme (4CA5) receptor in 2D form, in the flavonoid Apigenin test compound the amino acid residues that work on the active side are in the van der Waals bond ASP A:358, TYR A:360, TRP A:59, ASN A:66, THR A:92, GLU A:123, ARG A:124, ALA A:89, LEU A:132, ASN A:85, ASN A:136, for Alkyl (Pi-Alkyl) interactions working on ALA A:63, in Pi-Sigma interactions working on ILE A:88 and for Pi-Pi T-shaped interactions working on TYR A:62.

Visualization of molecular docking results of the flavonoid test compound Naringeninwith the Angiotensin Converting Enzyme (4CA5) receptor in 2D form, in the flavonoid Apigenin test compound, the amino acid residues that work on the active side are the van der Waals bonds TRP A:357, ASN A:70, VAL A:351, ALA A:356, PHE A:391, HIS A:387, ZN A:1001, ARG A:522, VAL A:518, HIS A:353, SER A:516, and hydrogen bonds work on the active side GLU A:143, HIS A:513, TYR A:523, GLU A:411, SER A:355, for the T-shaped Pi-Pi interaction works on PHE A:512.

The ACE enzyme has two essential types of binding sites: metal-binding sites and the active site. Based on [23], metal binding binds to zinc metal; the interaction involves amino acids HIS383, HIS387, and GLU411. The active site of the ACE enzyme is located at amino acid GLU384. Zinc ions are essential components of ACE because they bind to the active site. Seven ligands interact with critical amino acids according to natural ligands and have more negative values (free Gibbs and Ki) (Table 2).

ADMET Prediction

Pharmacokinetic assessment of flavonoids as oral drug candidates was performed using the pkCSM website. These tools allow the evaluation of key parameters in the ADMET profile: Absorption, Distribution, Metabolism, Excretion, and Toxicity. Through this approach, most of the studied flavonoids demonstrated adequate bioavailability and low toxicity (Wee et al., 2021). This indicates suggest a favorable safety profile in silico (Amin et al, 2024).

The absorption rate was measured at the PKCSM site, which has several parameters: water solubility, Caco-2 permeability, intestinal absorption, and P-gp substrate. Water solubility is the degree of solubility of a compound in water. The more negative the value, the more difficult it is to absorb. The water solubility categories are ≥0, highly soluble in water, 0 to -2, moderately soluble, -2 to -4, slightly soluble, and <-4, difficult or even insoluble (Sorkun et al., 2019). Caco-2 cells are used as an in vitro model of the human intestinal mucosa to predict the absorption of orally administered drugs. A compound is said to have high Caco-2 permeability if its permeability coefficient is >8x10 cm/s. For the pKCSM predictive model, high Caco-2 permeability will result in a prediction value >0.90 cm/s (Petrescu et al., 2019).

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Human intestinal absorption is the process by which drugs are absorbed from orally administered solutions. A compound with an absorbance of <30% is considered poorly absorbed (Pires et al., 2018). A P-gp substrate is a compound that will be pumped out by the P-gp protein because it is recognized as a foreign substance that is potentially harmful to the body (Juvale et al., 2022).

Table 3. Results of Absorption Profile Analysis of Test Compounds and Reference Ligands

Ligand Name	Water Solubility (log mol/L)	CaCO-2 Permeability (logPapp in 10 $^{-6}$ cm/s)	Human Intestinal Absorption (%absorbed)	P-gp substrate
Captopril	-1,522	1,179	79.769%	No
Kaempferol	-3.04	0.032	74.29%	Yes
Luteolin	-3,094	0.096	81.13%	Yes
Apigenin	-3,329	1,007	93.25%	Yes
Catechin	-3.117	-0.283	68.829%	Yes
Quercetin	-2,925	-0.229	77.207%	Yes
Naringenin	-3,224	1,029	91.31%	Yes

Based on the results obtained, all test compounds are slightly soluble, while the reference ligand captopril is quite soluble. In the Caco-2 permeability parameter, there are only two test compounds, namely Apigenin (1.007) and Naringenin (1.029), which have high Caco-2 permeability. This means that the absorption of the test compounds in the small intestine can proceed well, just like the reference ligand Captopril (1.179), because they can penetrate the intestinal epithelial layer. All compounds have good intestinal absorption, especially Apigenin (93.25%) and Naringenin (91.31%). Table 2 shows that all test compounds are recognized as P-gp substrates, indicating that the test compounds Kaempferol, Luteolin, Apigenin, Catechin, Quercetin, and Naringenin will be pumped out of the brain and back into the blood by P-gp when entering the BBB because they are recognized as foreign substances that are potentially harmful to the body (Juvale et al., 2022).

Volume of Distribution is the theoretical volume into which the total dose of a drug is distributed uniformly to provide the same concentration as in blood plasma (Pires et al., 2018). VDss is considered low if it is below 0.71 L/kg (log VDss <-0.15) and high if it is above 2.81 L/kg (log VDss >0.45) (Abdullah et al., 2021). The unbound fraction (Fu) is a measure of the proportion of a compound in the blood that is not bound to proteins. The higher the Fu, the greater the proportion of the compound that is free and active, thus improving its distribution to body tissues. The unbound fraction can affect renal glomerular filtration, liver metabolism, and volume of distribution and total clearance (Watanabe et al., 2018).

Table 4. Results of the Distribution Profile Analysis of Test Compounds and Reference Ligands

Ligand Name	Volume of Distribution (VDss) [log L/kg]	Fraction Unbound (FU)
Captopril	-0.939	0.678
Kaempferol	1,274	0.178
Luteolin	1,153	0.168
Apigenin	0.822	0.147
Catechin	1,027	0.235
Quercetin	1,559	0.206
Naringenin	-0.015	0.064

Based on Table 4, five test compounds have VDss that fall into the high category, namely Kaempferol (1.274), Luteolin (1.153), Apigenin (0.822), Catechin (1.027) and Quercetin (1.559), while the test compound Naringenin (-0.015) and the reference ligand Captopril (-0.939) fall into the medium

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category because 0.45 <VDss <-0.15. This indicates that the four test compounds, namely Kaempferol, Luteolin, Apigenin, Catechin, and Quercetin, have high distribution capabilities in the blood to the tissues. However, the test compound, Naringenin, and the reference ligand, Captopril, have moderate distribution capabilities. The distribution analysis using the FU parameter shows that all compounds have relatively low unbound fractions, indicating greater binding to serum proteins. However, in the distribution analysis, the VDss parameter is preferred over the FU parameter because it better describes the overall distribution of compounds in the body. A low FU value does not necessarily indicate poor distribution, as a small free fraction remains and can still interact with receptors.

Cytochrome P450 is an essential enzyme in the body, primarily found in the liver. Cytochrome P450 oxidizes xenobiotics to inactivate drug compounds. It is necessary to assess a compound's ability to inhibit cytochrome P450. Cytochrome P450 has several isoforms, including substrates for CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 (Abdullah et al., 2021).

Inhibitors of these enzymes are often used as markers of metabolism, as these five CYP450 enzymes play a crucial role in the metabolism of various compounds, particularly drugs. If a compound acts as an inhibitor of these enzymes, it can inhibit its own metabolism or disrupt the metabolism of other compounds that use the same enzyme pathway. This condition has the potential to cause drug interactions, decreased therapeutic efficacy, or even toxicity due to compound accumulation in the body. Furthermore, CYP450 enzymes also play a crucial role in converting some prodrugs into their active forms. Inhibition of these enzyme activities by inhibitors can disrupt the prodrug activation process, thereby reducing the effectiveness of therapies that depend on this conversion (Kiani & Jabeen, 2019).

Table 5. Results of Metabolic Profile Analysis of Test Compounds and Reference Ligands

Ligand Name	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor
Captopril	No	No	No	No	No
Kaempferol	Yes	No	No	No	No
Luteolin	Yes	No	Yes	No	No
Apigenin	Yes	Yes	No	No	No
Catechin	No	No	No	No	No
Quercetin	Yes	No	No	No	No
Naringenin	Yes	No	No	No	No

Based on the results of the cytochrome P450 enzyme metabolism profile in Table 5, the reference ligand Captopril showed the lowest toxicity risk, along with the catechin test compound; this is supported by its activity, which did not inhibit all cytochrome P450 enzyme substrates. Other test compounds showed diverse inhibition patterns, but no compound inhibited all P450 enzymes. Kaempferol inhibited CYP1A2, followed by Luteolin, Apigenin, Quercetin, and Naringenin. Further inhibitory activity was observed with Apigenin on the CYP2C19 substrate and with Luteolin on the CYP2C9 substrate. Thus, all test compounds were considered metabolically feasible, although caution should be taken when using them with other drugs that are metabolized from the same substrate as the inhibited substrate.

Organic cation transporter 2 (OCT2) is a renal uptake transporter that plays a crucial role in the renal uptake and clearance of drugs and endogenous compounds. OCT2 substrates also have the potential for adverse interactions when co-administered with OCT2 inhibitors. Assessment of potential candidates for OCT2 transport provides valuable information not only on clearance but also on potential contraindications. The proportional constant CL total reflects drug clearance and is the sum of hepatic clearance (metabolism in the liver and biliary clearance) and renal clearance (renal excretion) (Abdullah et al., 2021).

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Table 6 shows that neither the test compound nor the reference ligand is excreted via the OCT2 transporter in the kidney, so no potential drug interactions involving the OCT2 pathway were found. The total clearance values for each compound varied, with apigenin having the highest value and naringenin having the lowest. This variation reflects the rate of elimination of the compound, where the higher the clearance value, the faster the compound is excreted, and vice versa. This information is essential for assessing the potential for compound accumulation, especially with high doses or repeated use.

Table 6. Results of Analysis of Excretion Profiles of Test Compounds and Reference Ligands

Ligand Name	Total Clearance (log ml/min/kg)	Renal OCT2 Substrate
Captopril	0.306	No
Kaempferol	0.477	No
Luteolin	0.495	No
Apigenin	0.566	No
Catechin	0.183	No
Quercetin	0.407	No
Naringenin	0.060	No

Toxicity testing is conducted to identify the harmful effects of compounds on humans through acute or chronic exposure. Key aspects of predicting compound toxicity include hepatotoxicity, AMEX toxicity, and hERG I and II inhibitor genes (Mujtahid et al., 2024). AMES toxicity is used as a measure of a compound's potential to be mutagenic. This measurement is based on an experiment in which bacteria whose histidine has been isolated produce histidine again when a compound is added, thus classifying the compound as mutagenic, which is harmful to the body because it can cause cancer (Jain et al., 2018).

The liver is a vital metabolic organ, and its function must be maintained. Therefore, measuring a compound's liver toxicity is necessary. Hepatotoxicity is a parameter used to determine whether a compound causes liver damage (Astuty & Komari, 2022). The heart is also a toxicity parameter through the Human Ether-a-go-go-related gene (HERG). The HERG or KCNH2 is a gene that encodes a potassium ion channel in the heart, which plays a role in cardiac repolarization. If a compound inhibits the ion channel encoded by this gene, heart failure can occur (Lamothe et al. 2016).

Table 7. Results of Toxicity Profile Analysis of Test Compounds and Reference Ligands

Ligand Name	AMES Toxicity	Hepatotoxicity	hERG I, hERG II Inhibitors
Captopril	No	No	No
Kaempferol	No	No	No
Luteolin	No	No	No
Apigenin	No	No	No
Catechin	No	No	No
Quercetin	No	No	No
Naringenin	No	No	No

The results of the toxicity profile analysis of the test compounds and reference ligands against the AMES toxicity, hepatotoxicity, and hERG I/II inhibitor parameters are shown in Table 7. All test compounds and the reference ligand, captopril, showed negative results across all three parameters. This indicates that these compounds are not mutagenic (do not cause genetic changes) and do not pose potential liver or heart toxicity.

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CONCLUSION

Based on evaluations of physicochemical properties using Lipinski's rule, ADMET profile predictions, and molecular docking of 6 flavonoid compounds, it was found that some compounds have the potential to target the ACE receptor, such as Quercetin. Quercetin has potential because it has a low binding energy and an inhibition constant, and it forms many vital bonds that play a role in inhibiting the ACE receptor.

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