Jurnal Farmasi dan Ilmu Kefarmasian Indonesia
Pharmacy and Pharmaceutical Sciences Journal
Published by Faculty of Pharmacy Universitas Airlangga
OPEN ACCESS
E-ISSN 2580-8303
P-ISSN 2406-9388

Jurnal Farmasi dan Ilmu Kefarmasian Indonesia Vol. 11 No. 1 April 2024, 80-88
DOI: 10.20473/jfiki.v11i12024.80-88
Available online at https://e-journal.unair.ac.id/JFIKI/

Molecular Docking and Pharmacokinetic Studies of *Moringa oleifera* As Angiotensin-Converting Enzyme Inhibitors

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Submitted: 13 Juni 2023
Revised: 11 February 2024
Accepted: 7 March 2024

Abstract

Background: *Hypertension in pregnancy is a vascular disorder that occurs before pregnancy or arises during pregnancy that there were 30% of cases of maternal death. Moringa oleifera's potential to lower blood pressure can be utilized as an alternative antihypertensive during pregnancy, minimizing the risk of preeclampsia.* ***Objective****: The purpose of this study was to determine the molecular target of Moringa oleifera is intended to optimize pharmacodynamic activity based on the interaction pattern of the compounds with the ACE inhibitor (PDB ID: 1O86).* ***Methods****: Molecular docking is carried out using Autodock 4.0 program (AutoDock Tools).* ***Results****: According to the binding energy value and ACE inhibitory interaction, α-Rhamnopyranosyl, β-Sitosterol, and Sinalbin are prospective Moringa oleifera compounds as alternative antihypertensive. These potential compounds can inhibit ACE with binding energy -8.23; -9.27; -9.14 kcal/mol. Pharmacokinetic predictions reported that the potential compounds are absorbed in the intestine and indicates as molecules are tightly bound to plasma proteins and, as well as CYP3A4 and CYP2C9 inhibitors. The prediction of toxicity indicates that the potential compounds are classified as drug-induced acute liver failure with low carcinogens.* ***Conclusion****: α-Rhamnopyranosyl, β-Sitosterol and Sinalbin can be suitable lead compounds for synthetic drugs for antihypertensive agents.*

Keywords*: angiotensin-converting enzyme, molecular docking, Moringa oleifera*

How to cite this article:
Hasan, R. & Herowati, R. (2024). Molecular Docking and Pharmacokinetic Studies of Moringa oleifera As Angiotensin-Converting Enzyme Inhibitors. *Jurnal Farmasi dan Ilmu Kefarmasian Indonesia*, 11(1), 80-88. http://doi.org/10.20473/jfiki.v11i12024.80-88

P-ISSN: 2406-9388
E-ISSN: 2580-8303

INTRODUCTION

Maternal mortality ratio (MMR) is one of the health parameters in determining the degree of quality of women's health, especially pregnant women. MMR is one of the parameters in achieving development goals through indicators of improving maternal health with the main target being reducing the risk of maternal mortality during pregnancy. Maternal and Reproductive Health in 2013 stated that there were cases of death of 8000 mothers due to complications of pregnancy and childbirth. The main causes of death are bleeding, preeclampsia with hypertension, infectious diseases and indirect causes. The 2018 Basic Health Research stated that there were 30% of cases of maternal death caused by hypertension in pregnancy (Ministry of Health RI, 2018).

Hypertension in pregnancy is a vascular disorder is defined as blood pressure ≥140/90 mmHg on two or more measurements that occurs before pregnancy or arises during pregnancy or during the puerperium. Based on the International Society for the Study of Hypertension in Pregnancy (ISSHP) there are 4 categories of hypertension in pregnancy, namely preeclampsia, gestational hypertension, chronic hypertension and preeclampsia-chronic hypertension. Hypertension in pregnancy is the main cause of maternal death, as well as having other serious effects during childbirth. It was occurring in 5% of all pregnancies (Karthikeyan, 2015). In the United States the incidence was reaches 6 to 10%, where there are 4 million pregnant women and an estimated 240.000 are accompanied by hypertension each year. Hypertension is a risk factor for stroke and its incidence increases in pregnancy where 15% of maternal deaths are caused by intracerebral bleeding (Malha *et al*., 2018).

The angiotensin-converting enzyme (ACE) serves as essential for managing hypertension. The kidneys convert angiotensin I to angiotensin II through the renin-angiotensin-aldosterone pathway, which then activates bradykinin. Some synthetic ACE inhibitors, including captopril, lisinopril, ramipril, and enalapril, are frequently utilized to treat hypertension (Atlas, 2007). The number of ACE inhibitors regulated for medicinal usage highlights the value of rational drug design methodologies based on receptor structural understanding as well as molecular modeling methods. ACE inhibitors are used to control high blood pressure, prevent strokes, treat left ventricular dysfunction, congestive heart failure, and nephropathy; nevertheless, common side effects include persistent cough, headache, dizziness, weakness, increased uric acid levels, and so on (Nathisuwan and Talbert, 2002).

Methyldopa is recommended as a hypertension-lowering drug in pregnancy, even women of childbearing age with hypertension who want to become pregnant are advised to replace antihypertensive drugs with methyldopa or nifedipine, labetalol. It turns out that in research Calcium Canal Blockers are superior to methyldopa in the prevention of pre-eclampsia. Undesirable effects of methyldopa are sedation, drowsiness, dry mouth, depression, postural hypertension, rebound hypertension, withdrawal syndrome, and several autoimmune events (Kario et al., 2018). A prospective observational cohort study has been conducted on 261 first trimester pregnancies given methyldopa compared to 526 pregnancies without hypertension. The result was that there was no significant increase in adverse events between the two. It was concluded that methyldopa has no indication of a teratogenic effect, although caution is required in administering methyldopa in the first trimester of pregnancy (Hoeltzenbein *et al*., 2017).

The potential of Indonesia's natural ingredients has led to great public interest in using traditional medicine empirically. This data is supported by the many explorations of Indonesian traditional medicine in research. Moringa leaves (*Moringa oleifera*) was once a prima donna of traditional medicine with its various properties, ranging from treating allergies, rheumatic pain, rheumatism, wound infections, lowering blood sugar levels and uric acid levels to lowering blood pressure. Moringa leaf decoction can reduce systolic and diastolic blood pressure (Yanti and Nofia, 2020). Moringa leaves are rich in potassium so that sodium levels in the blood can be controlled, which has implications for reducing high blood pressure (Aminah, 2015).

The potential of Moringa leaves to lower blood pressure can be utilized as an alternative antihypertensive in pregnancy as a preventive step in suppressing the risk factors of preeclampsia. However, the identification of these active compounds against macromolecules or the molecular action targets for reducing blood pressure is not clearly and significantly known. Early identification of the target of molecular action and the mechanism of action of a chemical substance can facilitate the optimization of drug activity. Bioinformatics analysis is a method for identifying targets of molecular action by comparing the similarity of the chemical structure of a compound to various compounds whose targets are known in a database.

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Identification of the target of molecular action of an active compound is intended to optimize directed pharmacodynamic activity based on the interaction pattern of the drug with the target. The challenge faced in identifying the target of molecular action of an active compound and its interaction pattern is a long and costly testing process. One of the efforts to deal with this problem is a computational experiment through an in-silico method approach with molecular docking techniques. The rapid development and current advances in computational techniques allow for in silico tests to speed up the process of selecting compounds to be synthesized (Talele *et al*., 2010).

Molecular docking provides a scoring function through molecular mechanics in the form of repulsion, hydrogen bonding, electrostatics and desolvation, as well as scoring results that show the affinity of the ligand and the interaction model for the target protein as an indication regarding the mechanism of action of the tested compound (Forli *et al*., 2016). By utilizing the molecular docking technique, the target proteins of several chemical constituents of moringa which have pharmacological activity as lowering blood pressure can be predicted and identified precisely based on scores and models of ligand and protein interactions based on calculations using the AutoDock 4.0 program in AutoDock Tools. To predict the pharmacokinetic and toxicity profiles of various chemical constituents of moringa that can interact with antihypertensive therapy target proteins using the ADMETlab 2.0 webserver.

MATERIALS AND METHODS

Preparation of macromolecules and ligands

ACE Inhibitor (PDB ID: 1O86) were identified through SuperPred (https://prediction.charite.de/), which are webserver for target predictions of compounds. The macromolecule downloaded the structure from PDB (https://www.rcsb.org) in .pdb format (Muhammad and Fatima, 2015). Three-dimensional structure of compounds as the ligands that have been created with VegaZZ in .PDB format. The ligands were optimized with AutoDock Tools. The preparation is done through AutoDock Tools by separating the native ligand and water molecules, as well as adding hydrogen atoms (Wati *et al.*, 2020).

Validation method

Validation was carried out on the native ligand to find the right conformation. The previously prepared macromolecules were redocked with the native ligand. The docking conformation is subsequently aligned with the native ligand conformation on the crystallographic structure represented in root-mean-square deviation (RMSD). The RMSD value states that the conformational alignment of the structure is still acceptable with a value of less than 2.0 Å, if it is smaller or closer to the value 0 then the alignment value is getting better (Xuan *et al.*, 2011).

Molecular Docking

The docking is carried out using the AutoDock 4.0 program with AutoDock Tools (ADT). Setting docking with rigid macromolecular format as well as GA Runs (200) and Population Size (150). Then select the Output submenu for Lamarckian GA (4.2). The results docking all the test ligands resulted in $G_{binding}$ (kcal/mol) which was then analyzed and visualized using the Discovery Studio Visualizer Biovia to see the shape or model of the anchorage formed (Hasan *et al.*, 2023).

Prediction of Pharmacokinetic and Toxicity Parameters

Prediction of pharmacokinetic and toxicity profiles was carried out online using webform ADMET Lab (https://admetmesh.scbdd.com). It has been widely recognized that absorption, distribution, metabolism, excretion and toxicity of potential compounds be evaluated for systematical as well as some physicochemical properties and medicinal chemistry friendliness. It is done by entering the SMILES code of the ligands retrieved from PubChem and clicking ADMET. The webserver will automatically standardize the submitted SMILES characters and calculate all of the endpoints. The prediction results are primarily displayed in tabular format in the browser, with a 2D molecular structure and a radar plot summarizing the compound's physicochemical properties. Concrete predictive values are provided for regression model-predicted endpoints such as Caco-2 permeability and plasma protein binding, among others Xiangya, 2021).

RESULTS AND DISCUSSION

Macromolecules preparation is the step in preparing the test protein in the molecular docking process by downloading the .pdb format in Protein Data Bank. The macromolecules were selected based on the identification of the ability of the potential compounds to target hypertension molecular action *Angiotensin-converting enzyme* (ACE) through *Super Prediction Anatomical Therapeutic Chemical (ATC).* As training data for the machine learning models, compounds with known ATC codes and target relations were used in the form of molecular fingerprints generated through their associated SMILES representation. For predicting targets, an artificial algorithm that learns was trained for

P-ISSN: 2406-9388
E-ISSN: 2580-8303

each predictable target. The accuracy of the models was assessed using 10-fold cross-validation, with 82% of the target models obtaining at least 85% accuracy and only 5% scoring less than 70%. Due to the fact that the performance of the computational algorithms varies between targets, two different scores are reported, which produce the following outcomes: the probability that the input structure interacts with the target in question as determined by the corresponding machine learning hypothesis and the overall accuracy of the predictive algorithm (Gallo *et al.*, 2022).

The macromolecular requirements used are crystallographic structures (X-ray diffraction) with larger and more precise macromolecular structures. The conformational resolution value is also considered with a maximum RMSD value of 2.0 (Campbell, 2002). Downloaded macromolecules in .pdb format contain native ligand complexes and crystallized water molecules. The native ligand and water molecule must be removed from the macromolecule so as not to interfere with the molecular docking process. The native ligand is removed in order to obtain individual macromolecules that will be docked with the test ligand. Water molecules are removed because they can mediate the interaction between the test ligands and macromolecules which can affect the complexity of calculations in molecular docking. Additionally, the chemical environment is adjusted by removing non-residual amino acid molecules and adding charged atoms. Residues other than amino acids are removed because they can interfere with the interaction between the ligand and amino acid residues on the active site of the macromolecule. Removing residues other than amino acids needs to be reviewed if the macromolecule has a chromoprotein (Mg) or cofactor part that is retained in its main structure (Hypercube, 2002).

Macromolecule (ACE) with the identity PDB ID: 1O86 is the target protein chosen for first-line therapy in the treatment of hypertension, heart failure and myocardial infarction. This macromolecule with a crystallographic (X-ray diffraction) type of structure has formed a complex with lisinopril as the native ligand with a resolution of 2.0 Å (Natesh et al.,2003). Optimization of prepared macromolecules in Autodock Tools aims to determine parameters grid box. The grid box is analogous to the space where native ligands or active compounds can establish a conformation when anchored to macromolecule. The determination grid box was used to determine the coordinates of macromolecules' active sites. Arrangement grid box is done by setting the coordinates grid center and grid size (Rachmania et al., 2015). As for the coordinates grid center obtained are x= 40.935, y= 32.383 and z=47.285 with the setting grid size of 40x40x40.

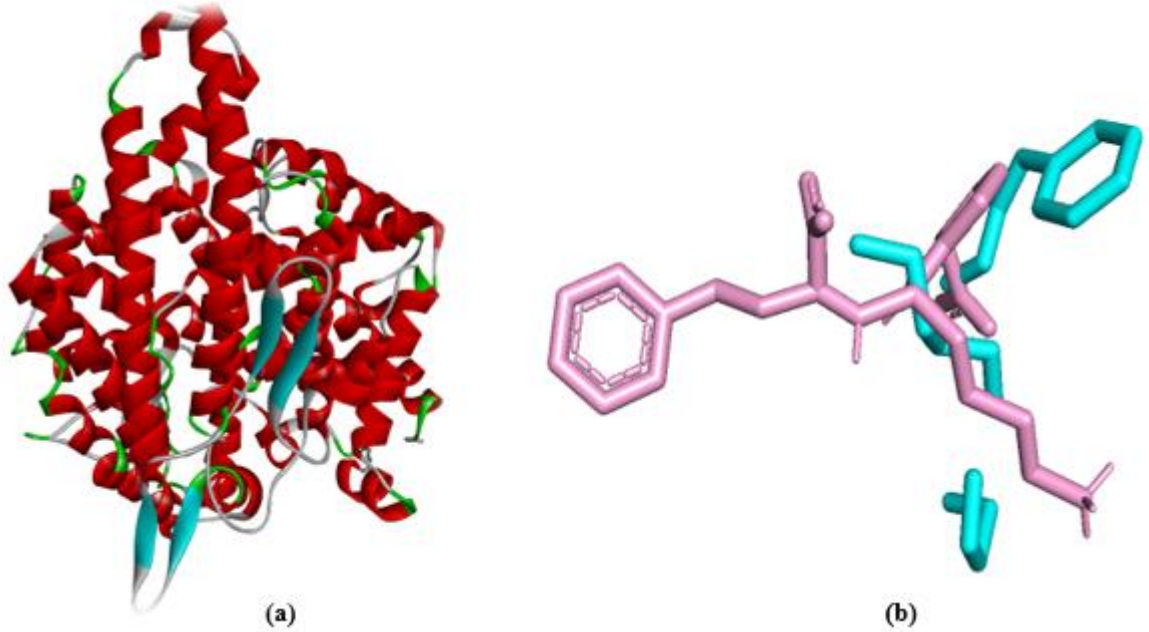


Figure 1. Macromolecule of ACE Inhibitor (PDB ID: 1O86) (a), Overlays of redocking ligand (pink) and reference ligand of crystallography data (blue) at 1O86 (b)

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Table 1. The results of molecular docking

Ligands	Bond energy (ΔG= kcal/mol)	Inhibitory constant (kI= uM)
Glucocochlearin	-6.48	17.93
Genistein	-6.65	13.44
Daidzein	-7.00	7.45
Niazirinin	-7.50	3.17
Niazidin	-7.38	3.88
Niazimicin	-7.10	6.24
Niazimin	-6.53	16.22
Niazine	-7.10	6.27
Niazim	-6.55	15.77
Niazicin	-6.68	12.70
α-Rhamnopyranosyl	-8.23	0.92452
Astragalin	-7.84	1.79
Vicenin	-3.76	1.75
Moringa	-5.67	69.70
β-Sitosterol	-9.27	0.15980
Hirsutrin	-7.55	2.91
Sinalbin	-9.14	0.20108
Amyrin	-5.65	72.43
Sitosteryl	-8.05	1.27
Chlorogenic	-7.68	2.33
Native ligand (Lisinopril)	-9.83	0.06216

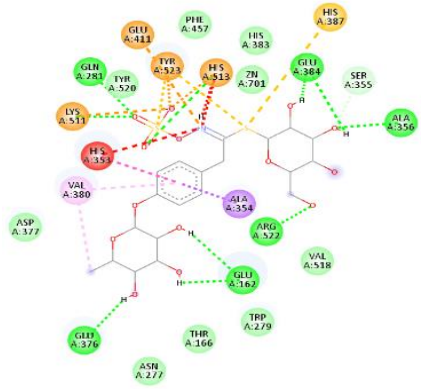
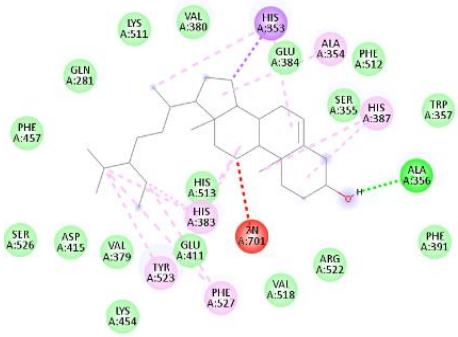
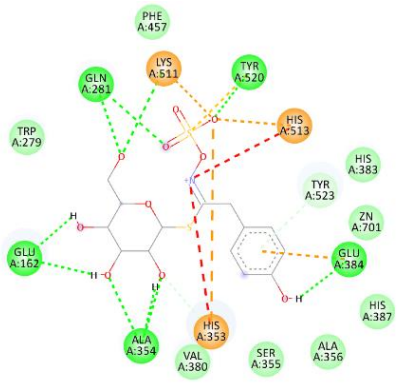
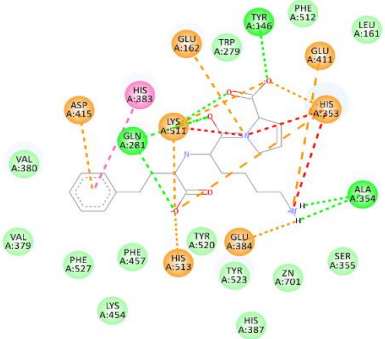
The structure of ligands is studied in order to obtain a structure that is more convergent or able to concentrate on the binding pocket of the receptor. This is based on the amount of active torsion possessed by each tested ligand. Lisinopril as the native ligand has a number of bond rotations of 13 torsion. α-Rhamnopyranosyl, β-Sitosterol and Sinalbin as the best test ligands had a number of bond rotations of 16, 7 and 12 torsions respectively. The large number of active torsions can determine the search time for the best conformation and the results of molecular docking are longer and more difficult to obtain. Determination of the amount of active torque is intended to determine the active bonds that can rotate during the docking process (Rachmania *et al*., 2015).

The molecular docking parameter that determines the accuracy of the method is the suitability of the type of interaction of the tested ligand to the macromolecule aligned with the type of interaction of the native ligand. Table 2 describes the types of interactions that appear in the test ligands α-Rhamnopyranosyl, β-Sitosterol and Sinalbin as the test ligands with the lowest bond energy values. The mechanism of inhibition of the ACE enzyme by the inhibitor lisinopril is in the presence of a carboxy-alkyl carboxylic group bond with a zinc atom on the active site of ACE. Hydrogen bonds appear on the Glu384 residue and the oxygen atom is opposite the zinc atom on the active site of ACE. Van der Waals bonds appear in the phenylpropyl group with residues Val518 and hydrogen bonds Glu162, Lys511 and Tyr520 (Natesh, *et al*., 2003). α-Rhamnopyranosyl makes an H-bond interaction with Glu384 and Glu162. α-Rhamnopyranosyl and Sinalbin are well positioned to bind to the active-site zinc atom. Zinc is an important catalytic component of ACE and bound at the active site. Sinalbin makes an H-bond interaction with Lys511 and Tyr520. β-Sitosterol contains hydrogen bonds, but the amino acid residues are not identical to native ligand.

α-Rhamnopyranosyl has a molecular weight of more than 500 Da so that it has 1 deviating value for the Lipinski parameter as a condition for a good drug compound. Drugs with a molecular weight of more than 500 Da can make it difficult for the drug compound to penetrate the cell membrane of the target receptor. Sinalbin and β-Sitosterol complied with the Lipinski rules similar to Lisinopril (Lipinski, 2001). SA score is a medicinal chemical parameter that indicates the ease with which a compound can be synthesized. The lower the SA score (<6) indicates that the compound can be easily synthesized into drug products. α-Rhamnopyranosyl has the largest SA score so it has characteristics that tend to be quite difficult to synthesize compared to the native ligand and other tested ligands (Grinter and Zou, 2014).

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Table 2. The similarity of bonding interactions between potential ligands and native ligand

Ligands	Hydrogen bond Interactions	Non-Hydrogen bond Interactions	Visualization
α-Rhamnopyranosyl	Glu384, Glu162, Glu376, Ala356, Arg522, Gln281	Phe457, Tyr520, His383, Ser355, Trp279, Asn277, Asp377, Glu411, Lys511, His513, Zn701	
β-Sitosterol	Ala356	Lys511, Val380, Lys454, Ser526 Phe457, His513, His383, Glu384, Ser355, Phe512	
Sinalbin	Gln281, Tyr520, Lys511	Phe457, Ala356, His387, Ser355, Tyr523, His513, His353, Lys511, Glu384, Val380, Trp279, Zn701	
Native ligand (Lisinopril)	Ala354, Gln281, Tyr146, Glu384	Phe457, Phe527, His387, Ser355, Tyr523, Tyr520, His513, His353, Lys511, Val379, Val380, Trp279, Lys454, Leu161, Zn701	

P-ISSN: 2406-9388
E-ISSN: 2580-8303

Table 3. Physicochemical parameters

Compounds	Physicochemical parameters						SA Score
	MW	nHA/nHD	nRot/nRing	Flex	TPSA	Log P	
Lisinopril	406.23	8/5	13/2	0.929	132.96	-1.535	3.172
α-Rhamnopyranosyl	571.10	15/8	9/3	0.429	245.26	-1.666	4.842
β-Sitosterol	414.39	1/1	6/4	0.300	20.230	7.663	4.388
Sinalbin	425.05	11/6	7/2	0.467	186.34	-1.130	4.225

Table 4. Pharmacokinetics and toxicity parameters

Compounds	Absorption		Distribution		Metabolism		Excrecy		Toxicity		
	Caco-2 Perm	HIA	PPB	VD	3A4 Inh	2C9 Inh	CL	$T_{1/2}$	DILI	ROAT	Carcino-genicity
Lisinopril	-6.194	+	19%	0.49	Yes	Yes	1.16	0.71	Yes	High	Low Carcinogen
α-Rhamnopyranosyl	-6.287	+	76%	0.65	Yes	Yes	0.78	0.23	Yes	High	Low Carcinogen
β-Sitosterol	-4.756	+	98%	1.96	Yes	Yes	16.6	0.01	Yes	Moderat	Low Carcinogen
Sinalbin	-6,163	+++	78%	0,32	Yes	Yes	0,74	0,61	Yes	Moderat	Low Carcinogen

Human Intestinal Absorption (HIA) is a parameter that describes the process of absorption in the intestine as a result of the bioavailability of absorption from the excretion ratio. An adequate HIA category is 20 – 70% (+) and good is 70 – 100% (++). The Caco2 parameter predicts the permeability of drug transport through intestinal epithelial cells derived from human colon adenocarcinoma with multiple transport pathways in vitro. The Caco2 cell parameter category is >70 nm/sec (high permeability); 4 – 70 nm/sec (medium permeability); <4 nm/sec (low permeability) (Cheng *et al*., 2013). Plasma Protein Binding (PPB) indicates that the drug molecule is tightly bound to plasma proteins. If the % PPB is below 90% it indicates that the molecule binds weakly to plasma proteins, and vice versa. The volume of distribution is a parameter that relates the drug concentration in blood plasma to the total amount of drug in the body. The optimal distribution volume parameter is 0.04 – 20 L/kg (Xiangya, 2021).

Drugs that are CYP2C19 and CYP2C9 inhibitors can increase plasma protein concentrations and sometimes cause side effects (Van Booven *et al*., 2010). CYP2D6 is responsible for the metabolism of most drugs and chemical compounds (Bertilsson *et al*., 2002). CYP2D6 is widely distributed in several tissues and is greatest in the liver (Ali et al., 2013). CYP3A4 is an enzyme that plays a major role in metabolism in the liver which is responsible for the oxidation process of small organic molecules, so they can be removed from the body (Dai *et al.*, 2001; Oyesakin *et al*., 2018).

Clearance (CL) is a parameter for determining the maintenance dose to achieve a desired plasma concentration or therapeutic concentration. High CL parameters with values >15 mL/min/kg and low CL values of <5 mL/min/kg. Half-life ($T_{1/2}$) is a parameter that predicts the time required for the drug level in the blood plasma to decrease to half the total level during the elimination phase. Short drug half-life is less than 3 hours and long drug half-life is more than 3 hours. All test ligands have short half-lives (Xiangya, 2021).

Drug induced liver injury (DILI) is a term that describes drug-induced acute liver failure. DILI is associated with direct dose-induced hepatotoxicity. There are two categories of hepatotoxicity, namely DILI with a high-risk category and no risk of hepatotoxicity. All potential compounds in Moringa leaves as antihypertensives are compounds with a risk of hepatotoxicity and are carcinogenic (Xiangya, 2021). Intravenous infusion of moringa extract at a dose of 40 mg/kg BW can reduce systolic pressure by 39.26 and diastolic by 20.79 mmHg in acetylcholine-induced rats (Mengistu, 2022). This is in line with research by Yanti and Nofia (2019), that Moringa leaf decoction can reduce systolic and diastolic blood pressure. Hypertension can be treated with Angiotensin Converting Enzyme Inhibitor (ACEI) drugs. ACE-Inhibitors inhibit the conversion of Angiotensin I to Angiotensin II resulting in vasodilation and decreased aldosterone secretion. In addition, the degradation of bradykinin is also inhibited so that blood levels of bradykinin increase and play a role in the vasodilatory

P-ISSN: 2406-9388
E-ISSN: 2580-8303

effect of ACE inhibitors. Vasodilation will directly reduce blood pressure, while reduced aldosterone will cause water and sodium excretion and potassium retention (Nafrialdi, 2009). β-Sitosterol reduced serum creatinine levels in rat kidneys induced hypertension (Cadmium chloride) at a dose of 1.3 mg/kg/day ($p<0.05$) (Olaiya *et al*., 2014).

CONCLUSION

A molecular docking research suggests that potential compounds from Moringa oleifera, such as α-Rhamnopyranosyl, β-Sitosterol, and Sinalbin might be effective antihypertensive drugs due to their binding energy and amino acid interactions with ACE inhibitors. The results showed that the potential compounds to inhibit ACE with binding energy -8.23; -9.27; -9.14 kcal/mol. Pharmacokinetic predictions reported that the potential compounds are absorbed in the intestine and indicates as molecules are tightly bound to plasma proteins and, as well as CYP3A4 and CYP2C9 inhibitors. The prediction of toxicity indicates that the potential compounds are classified as drug-induced acute liver failure with low carcinogens.

ACKNOWLEDGMENT

First and foremost, we would like to thank our primary supervisor, Dr. Rina Herowati, for her guidance, support, and encouragement throughout the entire process. Her mentorship and expertise were invaluable in helping us to shape the direction of our research and to bring our ideas to fruition.

AUTHOR CONTRIBUTIONS

Conceptualization, RA.H.; Methodology, RI.H.; Software, RI.H.; Validation RA.H.; Formal Analysis, RA.H.; Investigation, RA.H.; Resources, RI.H.; Data Curation, RI.H.; Writing - Original Draft, RA.H.; Writing - Review & Editing, RI.H.; Visualization, RA.H.; Supervision, RA.H.; Project Administration, RA.H.; Funding Acquisition, RA.H.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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P-ISSN: 2406-9388
E-ISSN: 2580-8303