Journal of Bio-Digital and Forensic Informatics (JBDFI)
Vol. 1, Issue. 2, 2026, pp. 17–27
DOI: XX.XX.XXXE-ISSN: xxxx-xxxx

Research

Molecular Docking Study of Mangiferonic Acid as a Potential Anti-Hypercholesterolemic Agent

Suci Ramadhani[1], Arafah Nurfadillah[2]*
[1] Biomedical Science Program, Faculty of Health Technology, Megarezky University, Makassar, Indonesia
[2] Bioinformatics Program, Faculty of Health Technology, Megarezky University, Makassar, Indonesia

Received: 15 June 2026
Revised: 13 July 2026
Accepted: 20 July 2026
Published: 28 July 2026

***Corresponding author:**
Arafah Nurfadillah
Bioinformatics Program, Faculty of Health Technology, Megarezky University, Makassar, Indonesia
Email: arafahnurfadillah@gmail.com

Abstract:
Introduction: Hypercholesterolemia is a major risk factor for cardiovascular disease. Mangiferonic Acid, a bioactive compound isolated from *Mangifera indica* L., has attracted attention as a potential natural inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. This study aimed to evaluate the anti-hypercholesterolemic potential of Mangiferonic Acid using an in-silico approach.
Methods: Biological activity was predicted using PASS Online based on the Probability of Activity (Pa) and Probability of Inactivity (Pi). Drug-likeness was evaluated according to Lipinski's Rule of Five. Molecular docking was performed using AutoDock Vina on the PyRx platform with the HMG-CoA reductase structure obtained from the Protein Data Bank (PDB), while the ligand structure was retrieved from the PubChem database. Binding affinity and ligand–protein interactions were analyzed, followed by pharmacokinetic and toxicity prediction through ADMET analysis.
Results: Mangiferonic Acid demonstrated a high predicted biological activity (Pa = 0.938) and satisfied most Lipinski criteria. Molecular docking revealed a binding affinity of −6.5 kcal/mol toward HMG-CoA reductase, with hydrogen bond interactions involving MET655 and VAL805 residues. ADMET analysis indicated high intestinal absorption (97.96%), favorable permeability, high plasma protein binding, and non-mutagenic and non-carcinogenic properties.
Conclusion: Mangiferonic Acid exhibits promising in silico anti-hypercholesterolemic potential through favorable binding interactions and pharmacokinetic characteristics. Nevertheless, further in vitro and in vivo studies are required to validate its efficacy and safety before therapeutic application.

Keywords: Mangiferonic Acid; HMG-CoA reductase; molecular docking; ADMET prediction; in silico drug discovery

1. Introduction

Hypercholesterolemia is a pathological condition characterized by elevated levels of total and LDL (Low-Density Lipoprotein) cholesterol in the bloodstream. This condition contributes to an increased risk of cardiovascular disease, which is a leading cause of morbidity and mortality globally. One of the main underlying mechanisms is the formation of atherosclerosis, driven by lipid accumulation and chronic inflammation in arterial walls. This process can lead to blockage of blood vessels, leading to severe clinical complications, such as myocardial infarction and stroke [1].

WHO data show that hypercholesterolemia is still a fairly high health problem in various countries. Globally, its prevalence in adults is recorded at 37% in men and 40% in women. The highest prevalence of elevated total cholesterol levels was observed in the Western European region, at about 54%, followed by the Americas at 48%. Meanwhile, the Southeast Asian region shows a relatively lower prevalence, which is around 30% in both sex groups [2]. BPS data in 2020 show that the proportion of Indonesians with cholesterol levels above normal values is higher in women (39.9%) than men (30%). This condition is expected to continue to increase along with changes in people's lifestyles. In the 2018 Basic Health Research, or called *Riskesdas* (*Riset Kesehatan Dasar* in Indonesian) 2022, the assessment of lipid status was carried out through the measurement of several clinical parameters, namely total cholesterol, HDL (High-Density Lipoprotein), LDL (Low-Density Lipoprotein), and triglycerides [3].

Cholesterol is a lipid molecule that plays an important role in maintaining the normal functioning of the body and is produced mainly by the liver. These compounds are the main components of cell membranes, particularly in nerve and brain tissues, and serve as precursors to various important biological compounds. In the body's circulation, cholesterol is found in the form of fatty acids and cholesterol esters [4]. Although necessary to support a variety of physiological activities, uncontrolled increases in cholesterol levels can be a major risk factor for cardiovascular disease. In general, cholesterol is transported in the blood by two main types of lipoproteins, namely HDL (High-Density Lipoprotein) and LDL (Low-Density Lipoprotein). LDL is atherogenic because it can settle on the walls of the arteries and trigger plaque formation, while HDL has a protective effect by helping transport cholesterol from peripheral tissues to the liver for further metabolism [3]. The use of hypolipidemic drugs, especially statins, is one of the main approaches in managing hypercholesterolemia. The mechanism of action of statins involves inhibiting the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which plays a role in the early stages of cholesterol biosynthesis in the liver. Inhibition of this enzyme will lower the production of endogenous cholesterol so that blood cholesterol levels, especially LDL cholesterol, can be effectively controlled [5]. The pharmacological approach is carried out by administering anti-hyperlipidemia drugs aimed at lowering blood cholesterol levels. Although effective, the continuous use of these drugs can cause unwanted side effects, including myopathy, impaired liver function, increased kidney workload, and the risk of kidney failure. Therefore, the development of non-pharmacological therapies based on natural ingredients is one of the interesting alternatives to be studied. One of the plants that has the potential to be used in an effort to lower cholesterol levels is mango (*Mangifera indica* L.), which is known to contain various bioactive compounds with anti-hypercholesterolemia activity [2].

Mango (*Mangifera indica* L.) is a plant that has high therapeutic value and has long been used in traditional medicine. Various parts of this plant are known to contain bioactive compounds that provide health benefits. Mango flowers contain tannins that have the potential to be used in the treatment of diarrhea, chronic dysentery, and several other health disorders. Mango fruit peel contains Alpha Hydroxy Acid (AHA), beta-carotene, as well as vitamins A, B, and C that function as antioxidants and support skin health. Meanwhile, mango seeds are traditionally used to help treat fever, diarrhea, chest pain, diabetes, and hypertension. In addition to the flowers, fruit peels, and seeds, other parts such as the bark, leaves, stems, and mangoes are also reported to have antibacterial activity, so they have the potential to be developed as a natural source of antibiotics [6]. Based on the results of phytochemical screening, mango leaves *(Mangifera indica* L.*)* It is known to contain several secondary metabolite compounds, including polyphenols, flavonoids, and triterpenoids. The presence of these compounds contributes to various biological activities of the mango plant. In addition, mangoes are a source of vitamin C, which functions as a natural antioxidant and plays a role in protecting the body's cells and tissues from damage due to oxidative stress caused by free radicals. The fiber content contained in mangoes is also suspected to have a hypocholesterolemic effect through its ability to help reduce cholesterol levels in the body [7]. The natural compounds contained in mangoes have prospects as an alternative to hypercholesterolemia therapy because they have the potential to provide lower side effects than statin drugs. Long-term use of statins is known to require

monitoring of liver and muscle function to anticipate the possibility of hepatotoxicity and myopathy. Considering these safety aspects, mango was chosen as the research object to evaluate the potential of its bioactive compounds as inhibitors of the HMG-CoA reductase enzyme through the molecular docking method, which is a computational approach in predicting the interaction between ligands and target receptors [5].

Molecular docking is a method used to predict interactions between receptor molecules and ligands using computational methods. This technique can be used as a reference and combined with in vitro and in vivo studies in drug discovery. The advantages of this technique are evident in its efficiency in terms of the time and financial resources required. The parameters used are bond affinity and residue similarity between the original ligand and the test ligand. The bond strength between the ligand and the receptor increases as the bond affinity value decreases. Residue similarity is defined as the degree of similarity of the test ligand to the original ligand in terms of binding to a protein [8]. Based on this description, this study aims to evaluate the potential of Mangiferonic Acid from *Mangifera indica* L. as an inhibitor of the HMG-CoA reductase enzyme through a molecular docking approach and ADMET analysis to support the development of natural material-based anti-hypercholesterolemia candidates.

2. Method

2.1 Research Location and Time

This research will be conducted in May-June 2026 at the Biomedical Science Undergraduate Study Program, Faculty of Health Technology, Megarezky University, Makassar, Indonesia.

2.2 Tools and Materials

This research was conducted using a computer device with a 64-bit Windows 10 operating system, an Intel® Core™ i5-8265U processor, 8 GB of RAM, and a Radeon 530 GPU. The software used includes ChemDraw Professional 17.1, PyMOL 2.6, PyRx, and BIOVIA Discovery Studio 2021. The research materials were in the form of Mangiferonic Acid compounds obtained from the PubChem database and the target protein structure of the HMG-CoA reductase enzyme obtained from the Protein Data Bank (PDB). Identification of Mangiferonic Acid compounds as bioactive metabolites of *Mangifera indica* L. was carried out through the KNApSAcK database.

2.3 Working Procedure

The overall in silico workflow consisted of sequential computational procedures designed to evaluate the anti-hypercholesterolemic potential of Mangiferonic Acid. The workflow began with biological activity prediction to identify the compound's pharmacological potential, followed by ligand preparation and drug-likeness evaluation to assess its physicochemical suitability as an orally active drug candidate. Subsequently, the target protein was prepared, and the molecular docking protocol was validated before docking simulations were performed to investigate ligand–protein interactions. The resulting docking complexes were further analyzed through molecular visualization, while pharmacokinetic and toxicity properties were evaluated using ADMET prediction. The complete workflow employed in this study, and each stage is described in detail in the following subsections.

a. Compound Prediction
   The bioactive compounds were obtained from the KnapSack (https://www.knapsackfamily.com/knapsack_core/top.php) site, and continued with a check on the potential of Mangiferonic Acid compounds on the PASS (Prediction of Activity Spectra for Substances) Online (https://way2drug.com/PassOnline/predict.php) website to see the Pa and Pi compounds.
b. Ligand Prep
   The preparation of the target 4HI ligand was carried out by downloading the 3D structure of the protein on the PubChem (https://pubchem.ncbi.nlm.nih.gov) page in *.sdf format. The ligand is further minimized and stored in *.pdb format.

c. Test Drug Likeness
Drug-likeness prediction is carried out to determine the physicochemical profile of the compound to be tested so that its ability as an oral preparation drug can be known. The ligands were drawn in the form of a 2D structure in the ChemDraw Ultra 12.0 software and then analyzed on the SwissADME (http://www.swissadme.ch/index.php) website. The test parameters include molecular weight, logP, donor hydrogen bond, and receptor hydrogen bond

d. Receptor Preparation
The target protein structure is obtained from the Protein Data Bank (PDB) with the code 3CCW. Receptor preparation is performed using PyMOL software by removing water molecules, native ligands, and unnecessary residues. The protein structure that has been prepared is then stored in PDBQT format for use in the molecular docking process.

e. Docking Method Validation
The docking process is carried out using PyRx Autodock. Before molecular tethering is carried out between the receptor and the test ligand and the comparator ligand, redocking between the receptor and the native ligand (AFO) is first carried out. The parameters used are: binding affinity value, binding type, bond distance, and amino acid residue.

f. Data analysis and validation of simulation results
The results of ligand and receptor docking were visualized in Biovia Discovery Studio 2021 both in 3D and 2D.

g. ADMET Analysis
ADMET (Adsorption, Distribution, Metabolism, Excretion, Toxicology) analysis was performed to determine the physicochemical profile and toxicity of the test compounds. The analysis was performed (https://preadmet.webservice.bmdrc.org/) and Toxtree software. The parameters analyzed through the PreADMET site in this stage include %HIA (Human Intestinal Absorption), Caco2 (Cancer coli-2), PPB (Plasma Protein Binding), BBB (Blood-Brain Barrier), and toxicity test results with Ames Test parameters.

3. Results

3.1 Prediction of Compound Potential

To obtain an initial assessment of the biological activity of Mangiferonic Acid, the compound was analyzed using the PASS Online server. The prediction was based on the Probability of Activity (Pa) and Probability of Inactivity (Pi) values, where a higher Pa than Pi indicates a greater likelihood of exhibiting the predicted biological activity. The prediction results for Mangiferonic Acid are presented in Table 1.

Table 1. Predicted biological activity of Mangiferonic Acid based on PASS Online analysis.

Compound Name	Formula	Pa Value	Pi Value
Mangiferonic Acid	$C_{30}H_{46}O_3$	0,938	0,002

3.2 Druglikeness Test

The drug-likeness properties of Mangiferonic Acid were subsequently evaluated using Lipinski's Rule of Five to assess its suitability as a potential orally active drug candidate. The evaluated parameters included molecular weight, lipophilicity (LogP), hydrogen bond donors, hydrogen bond acceptors, molar refractivity, and the number of Lipinski rule violations. The results of the drug-likeness assessment are summarized in Table 2.

Table 2. Drug-likeness properties of Mangiferonic Acid according to Lipinski's Rule of Five.

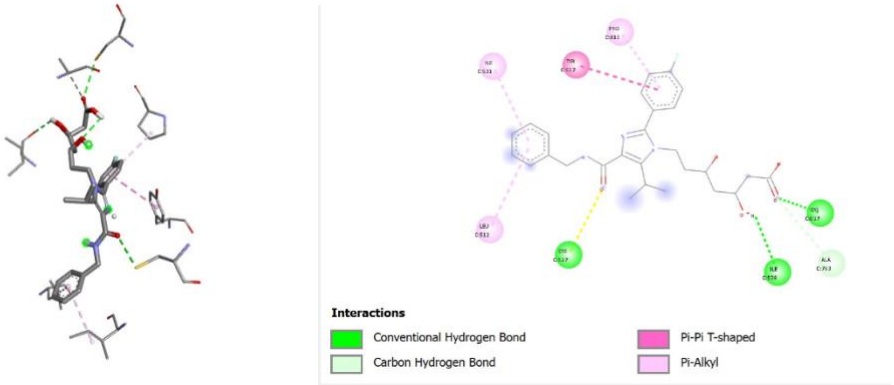
Compound Name	Mass (Molecular Weight)	LogP	HBD	HBA	MR
Mangiferonic Acid	454.68	4.19	3	1	135.95

3.3 Molecular Docking

To investigate the interaction between Mangiferonic Acid and the target enzyme, molecular docking simulations were performed against HMG-CoA reductase. The docking analysis evaluated binding affinity as well as the key amino acid residues involved in ligand–protein interactions at the active site. The molecular docking results are presented in Table 3, as well as illustrated computationally in Figure 1.

Table 3. Molecular docking results of Mangiferonic Acid against HMG-CoA reductase, including binding affinity and key ligand–protein interactions.

No.	Compound Code	Binding Affinity	RSMD	Amino acid residues	Types of Bonds
1	4HI	-7,1	0	CYS527 ILE536 CYS817	Conventional Hydrogen Bond
				PRO813 ILE531 LEU512	Pi-Alkyl
				ALA763	Carbon Hydrogen Bond
				TYR517	Pi-Pi T-shaped
2	Mangiferonic Acid	-6,5	0	MET655 VAL805	Conventional Hydrogen Bond
3	Simvastatin	-7,3	0	ILE762	Carbon Hydrogen Bond
				PRO355	Alkyl
				TYR533	Pi-Alkyl



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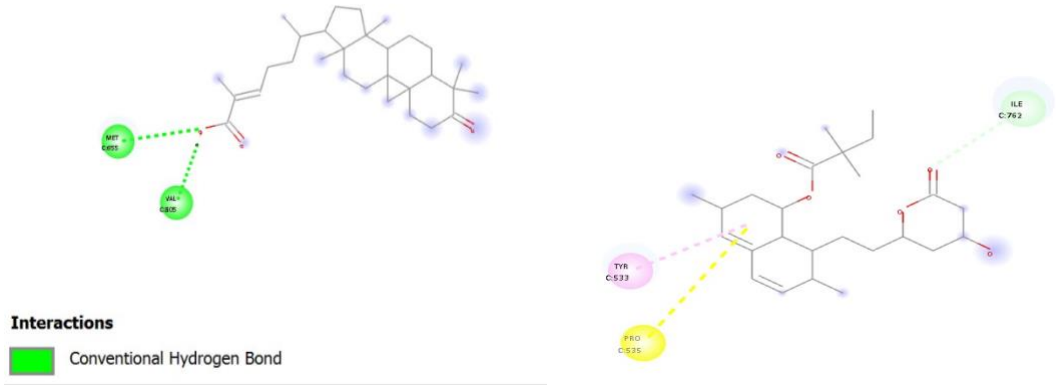

Figure 1. Molecular simulation of (A) 3D interaction of receptors and natural ligands, (B) 2D interactions of natural receptors and ligands, (C) 2D interactions of receptors and test compounds, (D) 2D interactions between receptors and comparator compounds.

3.4 ADMET Analysis

To complement the molecular docking results, pharmacokinetic and toxicity properties of Mangiferonic Acid were predicted using computational ADMET analysis. This stage aimed to evaluate the compound's absorption, distribution, metabolism, excretion, and toxicity profiles, providing preliminary insight into its potential safety and drug development feasibility, as seen in Table 4.

Table 4. ADMET Mangiferonic shaft analysis results

Compound	Absorption		Distribution			Toxicity		
	Caco-2 Permeability (nm/s)	Human Intestinal Absorption (HIA, %)	Plasma Protein Binding (PPB, %)	Blood–Brain Barrier (BBB)	P-glycoprotein Inhibitor	Kroes TTC Class	Carcinogenicity	Mutagenicity (Ames Test)
Mangiferonic Acid	13.19	97.96	94.0	0.81	Yes	Class III	Negative	Negative

4 Discussion

4.1 Prediction of Compound Potential

Mangoes are fruits belonging to the Anarcadiaceae family, which were historically cultivated in India about 4000 years ago. The results of phytochemical screening of mango leaves contain polyphenols, flavonoids, and triterpenoids. Mangoes contain a lot of vitamin C, which acts as an antioxidant, so that when cell or tissue damage occurs, this Vitamin C can protect from the cause of oxidative stress [9]. Mango (*Mangifera indica* L.) It also contains fiber that is thought to play a role in lowering cholesterol levels [7]. Based on the selection results from the KNApSAcK database, one compound that meets the criteria for further analysis was obtained, namely Mangiferonic Acid.

Prediction of the potential of compounds is carried out to determine the properties and biological activities of a compound, especially related to its use as a drug and natural ingredient. The parameters used in this analysis include the value of Pa (Potential Activity) and Pi (Potential Inactivity). Predictions of plant compound activity are obtained through the site Way2Drug PASS Online [10]. The results of the analysis of the potential of Mangiferonic acid compounds as anti-hypercholesterol are presented in Table 1.

Based on Table 1, Mangiferonic Acid compounds show a value of Probability of Activity (Pa) of 0.938 and a value of Probability of Inactivity (Pi) is 0.002. The Pa parameter describes the degree of probability that a compound has a certain biological activity, while Pi indicates the probability that the compound does not exhibit the predicted activity. This assessment was obtained through analysis

using the PASS method (Prediction of Activity Spectra for Substances), which predicts biological activity based on the similarity of a compound's structure to a database of known compounds [10].

The prediction results show that the value of Pa in Mangiferonic Acid much higher than the value of Pi. This condition indicates that the compound has a very strong probability of displaying the expected biological activity. In addition, a Pa value exceeding the 0.7 limit indicates a high level of predictive confidence, so Mangiferonic Acid has the potential to be further developed as a candidate for bioactive compounds. The very low Pi value further strengthens the suspicion that this compound has a low probability of being inactive to predicted biological targets [11].

4.2 Druglikeness Test

The drug likeness test is a method used to predict the suitability of a compound as a drug candidate based on *Lipinski's Rule of Five*, by conducting a virtual screening of potential compounds based on similarity in physicochemical properties or structure [12]. From 1 *Mangifera indica* L plant compound, only 1 test compound was selected for the drug likeness test. This is because only 1 compound is available in the data. The results of the drug-likeness test for Mangiferonic acid and the native ligand 4HI can be seen in Table 2. Five parameters must be met, namely: having a Mass of <500 D, hydrogen bound donors (HBDs) not more than 5, Hydrogen Bound Acceptors (HBAs) not more than 10, having a logP of not more than 5, and Molar refractivity between 40 and 130 [13].

Based on Table 2, the Mangiferonic Acid compound has a molecular mass of 454 Da, so it meets the criteria *Lipinski's Rule of Five* because it does not exceed the limit of 500 Da. The molecular mass within that range indicates that the compound has the potential to have good permeability and absorption, as molecules that are too large are generally more difficult to penetrate the cell membrane [13]. The Hydrogen Bond Donor (HBD) value of Mangiferonic Acid of 3 also meets the requirements of Lipinski (<5). An appropriate amount of hydrogen donors can support the formation of hydrogen bonds without excessively increasing polarity, which can inhibit oral absorption. In addition, the Hydrogen Bond Acceptor (HBA) of 1 is still below the maximum limit of 10, so it is estimated that it does not interfere with the membrane permeability and the absorption process of compounds in the body [14].

However, the value of molar refractivity of Mangiferonic Acid of 135.95 slightly exceeds the recommended range (40–130). High values indicate the larger size and polarizability of molecules, which can affect the process of absorption, distribution, and transport of compounds in the body. However, since there was only one violation of Lipinski's rules, Mangiferonic Acid still has good potential as a drug compound candidate and is worthy of further research [8].

4.3 Molecular Docking

Target ligands and proteins that have gone through the preparation stage are then used in the molecular docking simulation using PyRx software with the AutoDock algorithm [15]. Protein preparation is carried out by removing water molecules, residues that do not play a role in the binding process, as well as the native ligand, which is still bound to the structure of the protein. This stage aims to produce a more representative model of the receptor so that the prediction of the interaction between ligands and target proteins can be done with a better level of accuracy. The removal of water molecules can also reduce the complexity of calculations during the docking process [16].

At the protein preparation stage, hydrogen atoms are added to complete the receptor structure. This addition is necessary because hydrogen atoms play an important role in the formation of hydrogen bonds, which is one of the key interactions in ligand binding to target proteins. Meanwhile, the preparation of the ligands is carried out through an energy minimization process to obtain the most

stable molecular conformation. A conformation with the lowest energy is generally closer to biological conditions, so that it can increase the reliability of the docking simulation results [17].

The parameters evaluated in this study include the value of Affinity, Root Mean Square Deviation (RMSD), the type of interaction formed, the amino acid residue involved, and the type of bond in the binding region [18]. Based on the results presented in Table 3, the binding affinity value of Mangiferonic Acid (–6.5 kcal/mol) showed a fairly good binding affinity to HMG-CoA reductase, although it was still lower than that of Simvastatin (–7.3 kcal/mol). This difference suggests that Mangiferonic Acid has the ability to bind to the active site of the enzyme, but the stability of the complex formed is still below that of the comparator drug.

The RMSD value is used to assess the suitability of the docked ligand pose to its reference conformation. The lower the RMSD value obtained, the closer the position of the predicted ligand is to the ligand conformation in the crystal structure, so that the docking results are considered more accurate. In general, the docking method is declared to have good validity if it produces an RMSD value of ≤ 2 Å [19]. Based on table 3 In the native ligand 4HI, the amino acid residues that interact include CYS527, ILE536, CYS817, PRO813, ILE531, LEU512, ALA763, and TYR517. The interactions formed consisted of conventional hydrogen bonds, Pi-Alkyl, carbon-hydrogen bonds, and Pi–Pi T-shaped. Conventional hydrogen bonds formed with CYS527, ILE536, and CYS817 residues play an important role in improving binding affinity and maintaining the stability of the complex [20]. The Pi-Alkyl interaction with PRO813, ILE531, and LEU512 residues is a hydrophobic interaction that helps maintain the position of the ligands in the binding site. In addition, the ALA763 residues form a carbon- hydrogen bond, while the residue of TYR517 forms the Pi–Pi T–shaped interaction, which contributes to the stability of protein–ligand complexes [21]. On Mangiferonic Acid, only two amino acid residues involved in binding were found, namely MET655 and VAL805. The interaction formed is in the form of a Conventional Hydrogen Bond. These hydrogen bonds show an affinity between the ligand and the receptor, but the number of residues involved is relatively less than that of the native ligand and the comparator ligand. This is in line with the fact that Mangiferonic Acid is lower than Simvastatin, so it shows a fairly good but not optimal interaction stability [8].

Meanwhile, Simvastatin interacts with ILE762, PRO355, and TYR533 residues. The types of bonds formed include Carbon Hydrogen Bond, Alkyl, and Pi-Alkyl. Alkyl and Pi-Alkyl interactions are hydrophobic interactions that play a role in strengthening ligand binding on the active side of the receptor. The presence of several of these hydrophobic interactions is thought to contribute to the affinity Simvastatin is the lowest (–7.3 kcal/mol), which shows a stronger binding affinity than Mangiferonic Acid and native ligands [20].

4.4 ADMET Analysis

Based on the results of ADMET prediction in Table 4, Mangiferonic Acid exhibits pharmacokinetic characteristics that support its development as an oral drug candidate. The parameters evaluated include absorption, distribution, and toxicity, which play an important role in determining the success of a compound to achieve biological targets as well as producing the expected therapeutic effect. In terms of absorption, Mangiferonic Acid has a $CaCO_2$ permeability value of 13.19, which indicates a good ability to pass through the intestinal epithelial membrane. The $CaCO_2$ model is one of the parameters commonly used to predict the permeability and absorption of drugs orally. High permeability values indicate that the compound has the potential to be effectively absorbed through the digestive tract [22].

A value of Human Intestinal Absorption (HIA) of 97.96% indicates that most of the compound is predicted to be absorbed into the human gut after oral administration, thus supporting good bioavailability. HIA is the sum of bioavailability and absorption evaluated from the ratio of excretion

through urine, bile, and feces. Most anthocyanidins have a percentage of HIA that is in the well-absorbed range, i.e., in the 70-100% range [23].

On the distribution parameters, Mangiferonic Acid shows a Plasma Protein Binding (PPB) value of 94.0%, which indicates that most of the compound molecules bind to plasma proteins. High binding to plasma proteins can prolong the circulation time of compounds in the blood and affect distribution to target tissues. However, only the free fraction can exert a direct pharmacological effect. Therefore, high PPB values need to be considered in the interpretation of the biological activity and pharmacokinetic profile of the compound [23]. A BBB value of 0.81 indicates that Mangiferonic Acid is predicted to have penetration ability into the central nervous system. Although these characteristics are not directly related to hypercholesterolemia therapeutic targets, they are important for describing the overall distribution profile of the compound [24].

The predicted results also show that Mangiferonic Acid has the potential to be a P-glycoprotein (P-gp) inhibitor. P-gp protein is an efflux transporter that functions to pump various compounds out of cells and plays a role in reducing the accumulation of drugs in certain tissues, including the brain. Inhibiting activity against P-gp can improve the retention and bioavailability of compounds because it reduces the efflux process carried out by the transporter. Therefore, the P-gp inhibitor properties in Mangiferonic Acid have the potential to increase pharmacological effectiveness through increased concentrations of compounds on biological targets [24].

Toxicity evaluation showed that Mangiferonic Acid had a predicted safe Ames test and did not show carcinogenic or mutagenic potential. These results indicate that the compound is not expected to cause damage to genetic material or trigger the formation of cancer. A good toxicity profile is one of the important requirements in the development of drug candidates as it relates to the safety of long-term use. Thus, the results of the toxicity prediction show that Mangiferonic Acid has a good enough level of safety to be studied further [23].

Overall, the results of ADMET analysis show that Mangiferonic Acid has a promising pharmacokinetic profile, characterized by high intestinal permeability, excellent oral absorption, adequate distribution ability, and a relatively safe toxicity profile. These findings support the potential of Mangiferonic Acid as a viable bioactive compound candidate to be further developed through in vitro and in vivo testing to verify its biological activity and safety.

Conclusion

Based on the results of the study, the compound Mangiferonic Acid derived from *Mangifera indica* L. shows potential as an anti-hypercholesterolemia candidate based on the in silico approach. The results of the prediction of biological activity showed a high activity value, supported by drug-likeness characteristics that met most of Lipinski's criteria. Molecular docking simulations show that Mangiferonic Acid is able to interact with the enzyme HMG-CoA reductase through the formation of hydrogen bonds and has a fairly good binding affinity. In addition, ADMET analysis showed a supportive pharmacokinetic profile, including high oral absorption, adequate distribution, and no mutagenic or carcinogenic potential. Thus, Mangiferonic Acid has the potential to be developed as a natural anti-hypercholesterolemia compound, although further research through in vitro and in vivo tests is still needed to confirm its effectiveness and safety.

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