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Potential Bioactive Compounds of Mahogany Seeds *(Swietenia mahagoni* Jacq.*)* as Antidiabetics through Computational Studies *in Silico* Molecular Docking

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ABSTRACT

Diabetes is a chronic endocrine metabolic disorder in insulin production or insulin resistance. Mahogany seeds are plants that have bioactive compounds that can treat diabetes mellitus. This study was conducted to determine the interaction between bioactive compounds of mahogany seeds and the Protein Tyrosine Phosphatase-1B (PTP1B) receptor with PDB ID code: 1T49. Bioactive compounds from mahogany seeds were subjected to docking simulations of 15 compounds with the reference ligand glibenclamide. In silico studies showed an interaction between bioactive compounds of mahogany seeds and PTP1B, the results obtained were in the form of binding energy between the ligand and the target protein. The compound with the best binding energy value was MSC15 (Chisocheton) with a binding energy value of -8.86 kcal/mol. The PyMOL program was used to visualize the 3D conformation of the molecule and ligand-protein interactions, the output was in the form of a Root Mean Square Deviation (RMSD) value of 1,363 Å show good value. The mahogany seed test ligand was also tested pharmacokinetically using the website https://preadmet.bmdrc.kr/ ,Pharmacokinetic parameter tests showed that mahogany seed compounds have excellent intestinal absorption (HIA >90%), strong plasma protein binding (>80%), and variable clearance rates, indicating high potential as an antidiabetic candidate.

Keywords: Diabetes, Docking, PTP-1B, Seeds mahogany

INTRODUCTION

Diabetes melitus is a group of metabolic diseases characterized by hyperglycemia that occurs due to abnormalities in insulin secretion, insulin action or both (Perkeni, 2015). Insulin is a hormone that can regulate blood glucose levels and facilitate glucose energy consumption in most cells. It is stored in the liver and fat tissue as glycogen. Other hormones that can also affect blood glucose levels include glucagon, amylin, cortisol, epinephrine, and growth hormone (Joshi & Khardori, 2021).

Uncontrolled diabetes causes serious disorders of the cardiovascular system, reduces quality of life, and premature death (WHO, 2016). There are three main types of diabetes mellitus (DM), namely type 1 DM due to the body's failure to produce enough insulin/insulin-dependent diabetes mellitus/juvenile diabetes; type 2 DM begins with insulin resistance, where cells fail to respond properly to insulin. As the disease progresses, insulin deficiency can also occur. The main causes are being overweight and not exercising. In addition to type 1 and type 2 diabetes mellitus, there is also gestational diabetes. Gestational diabetes is the third form and occurs in pregnant women with no prior history of diabetes who experience high blood glucose levels. Gestational diabetes is the third form and occurs in pregnant women without a previous history of diabetes who experience high blood glucose levels (McIntyre *et al*., 2019).

Diabetes drugs such as metformin, pioglitazone, sulfonylureas, biguanides, glimepiride and glibenclamide can cause gastrointestinal problems (nausea, diarrhea, abdominal pain), fatigue, headaches, and myalgia (muscle pain). Insulin is used by injecting it into the abdominal area, this can cause side effects such as hypoglycemia (low blood sugar), digestive problems (nausea, vomiting, diarrhea), chills, and sweating. The search for a major drug agent that can modulate important receptor targets that have an effect on improving insulin sensitivity in several human

diseases and disorders, such as diabetes, obesity, and hematopoietic malignancies, through the modulation of different signaling pathways (Liu *et al*., 2022).

The side effects of using synthetic drugs have made people trust to consume natural medicines. Medicinal plants can have many bioactives in them, one of which is the mahogany seed plant. Therefore, this study aims to determine the binding affinity and interaction produced between the bioactive compounds of mahogany seed plants and the PTP1B receptor. Previous research has shown that in vivo testing can lower random blood sugar levels in male Wistar rats (Sinurat & Budi, 2023). Furthermore, in vitro testing has also shown that mahogany seeds have antidiabetic activity (W, 2021).

Mahogany seeds *(Swietenia mahagoni Jacq)* are widely used as medicine in India, several African countries and also in Indonesia. Traditionally used for malaria, hypertension, diabetes, cancer, cough, and diarrhea. BM has main bioactive compounds, namely flavonoids, saponins, alkaloids (Krishna & Maurya, 2018) and triterpenoids (Wresdiyati *et al*., 2015). In the ether extract, BM is known to contain 28 tetranotriterpenoids, which are associated with switenia and swietenolide compounds (Naveen *et al*., 2014). The function of this compound is known to have antidiabetic activity (Rahman *et al*., 2009).

The pharmacological activity of BM extract varies, including antibacterial, antimalarial, anti-hepatitis, anticancer, antidiabetic, anti-inflammatory, and antimutagenic (Telrandhe *et al*., 2022). Several studies have shown that mahogany seeds (Swietenia mahagoni Jacq) have antidiabetic activity. Mahogany seeds contain saponins, flavonoids, alkaloids, terpenoids, cardiac glycosides, anthraquinones, and volatile oils. There is a flavonoid compound in mahogany seeds called swietenin which functions as a hypoglycemic agent.

The swietenin compound in mahogany seeds (Swietenia mahagoni Jacq) refers to the class of tetranortriterpenoid compounds that have antidiabetic activity (Wulansari & Wulandari, 2018). This test was carried out using the in silico molecular docking method, where the test looks at the bond between the bioactive compounds of mahogany seeds and the target protein.

RESEARCH METHODS

Tools and materials

Computational study *of in silico molecular docking* was conducted using *a computer proAMD A8-7410 APU with AMD Radeon R5 Graphics 2.20 GHz* with 4 GB RAM. Assisted by offline and online software, namely MarvinSketch 15.5.11, Chimera 1.10.2, pymol 2.3.3, Rasmol 2.7.5, Discovery studio V21.1.0.20298, Autodock 4.2., PreAdmet, molsoft.com, and way2drug.com. The materials used are active compounds of mahogany seeds and macromolecular targets, namely Protein Tyrosine Phosphatase-1B (PTP-1B).

In Silico Study

The study used a *virtual screening test* with a computational study through an *in silico molecular docking approach* of the bioactive compounds of mahogany seeds against PTP-1B. The in silico molecular docking process begins with tracing the target protein on the Protein Data Bank website. After the target protein to be used is known, it is then downloaded in pdb format, the pdb code used is 1T49, which will then be optimized and separated (Humaedi & Halimatushadyah, 2021) between the ligand and its receptor to interact with the bioactive compounds of mahogany seeds and the separation of non-standard residues.

The next stage is to prepare the ligand by creating 2D and 3D structures and adding hydrogen atoms and Gasteiger energy. The next stage is to dock the grid box coordinates with the Grid center size X = 55.319, Y = 31.908, Z = 22.447. Each ligand is in a flexible condition that will interact with macromolecules in rigid conditions. Furthermore, Grid Parameter File (GPF) and Docking Parameter File (DPF) files were created for macromolecular complexes with ligands. Next is the docking simulation process, with runs 100. The last stage is the analysis and visualization of the docking simulation results. Pharmacokinetic studies are conducted by looking at ADME parameters that can be viewed on the website https://preadmet.bmdrc.kr/.

RESULTS AND DISCUSSION

Characteristics of bioactive compounds in ahogany seeds

The search for bioactive compounds was obtained from the results of previous studies, which were then analyzed based on molecular weight, the number of hydrogen donors, and c Log P. The logP value is related to the polarity of the compound, namely the magnitude of the logP value is directly proportional to the hydrophobic properties of the molecule. If the molecule is too hydrophobic, then its toxicity tends to be higher because it is easily distributed more widely in the body, causing reduced selectivity of the bond to the target protein.

The number of donor and acceptor hydrogen bonds shows that the higher the hydrogen bond capacity, the higher the energy required for an absorption process to occur (Syahputra, 2014).

The characterization analysis of the bioactive compounds used Marvinsketch 15.5.11 software. The screening results of the mahogany seed bioactive compounds were then used as ligand compounds that would interact with the target protein, namely Protein Tyrosine Phosphatase-1B (PTP-1B). PTP-1B plays a role in modulating insulin signal transduction. PTP-1B can also be a major regulator of insulin receptor activity, acting on insulin receptors and on insulin signaling components. According to Ya-Qian Ma in 2018 (Ma *et al*., 2018), mahogany seeds have 15 bioactive compounds, the structure of the compound can be seen in the picture and its characteristics can be seen in the Table 1.

Table 1. Characteristics Test Compound Seeds Mahogany

No.	Test Ligand	Code	Molecular Weight	C Log P	Donor hidrogen	Acceptor hidrogen
1	Swietemacrolides A	MSC1	627.795	1	-	8
2	Swietemacrolides B	MSC2	625.779	1	-	8
3	Swietemacrolides C	MSC3	502.560	1	3	2
4	Swietemacrolides D	MSC4	516.631	4	2	8
5	Swieteliacate D	MSC5	502.560	2	3	6
6	Swieteliacate B	MSC6	611.840	1,35	-	6
7	Swietemahonin F	MSC7	635.852	1,35	-	7
8	Mahagonin	MSC8	693.354	1	-	8
9	7-desacetylgedunin	MSC9	456.579	2,94	3	5
10	7-deacetoxy-7-oxogedunin	MSC10	472.578	2,94	4	6
11	6a-acetoxyepoxyazadiradione	MSC11	524.610	3,93	-	7
12	Andirobin	MSC12	468.546	4,18	-	6
13	Methyl angolensate	MSC13	456.535	3,63	-	7
14	Secomahoganin	MSC14	528.598	3,97	-	2
15	Chisocheton	MSC15	530.746	4,25	2	6

Note : Mahogany Seed Compound (MSC)

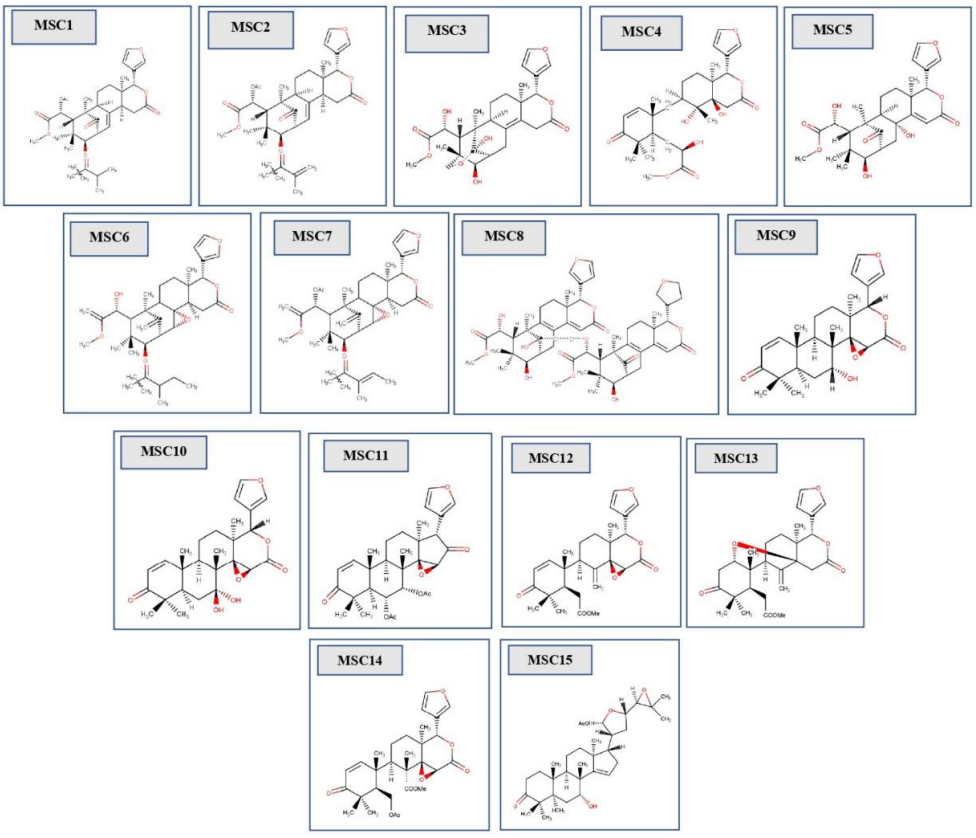

Figure 1. Structure Of The Test Ligan

Docking simulation

The target macromolecule used is PDB ID: 1T49. Ligands and proteins were obtained and prepared so that they succeeded in obtaining proteins without ligands and native ligands. Proteins and ligands were prepared using Chimera software in order to obtain the integrity of the 3D molecular geometry of the target protein from the chain taken. This was done to meet the needs of the algorithm in performing molecular docking.

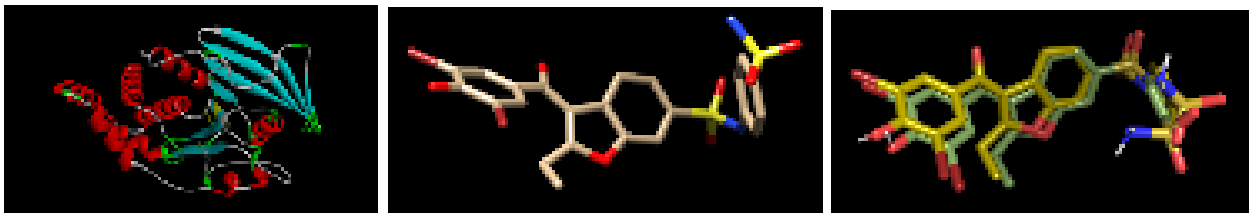

Figure 2. PTP-1B receptor (A), Native ligand (B), RMSD of native ligand (C)

Docking simulation analysis was carried out to determine the interaction between the ligand compound and the target protein. The resulting binding energy value can describe how strong the bond between the ligand compound and the target protein is. The lower the binding energy value, the more stable the resulting bond will be. Analysis of the correct docking simulation protocol is one of the keys to success in obtaining valid docking poses (Oniga *et al*., 2017).

Validity evaluation is carried out by determining the Root Mean Square Deviation (RMSD) value, this is done to describe how far the state of the protein complex with the ligand changes over time (Lestari *et al*., 2023). RMSD (Root Mean Square Deviation) is a parameter used to determine whether the docking process parameters are running correctly or not, and describes how much the natural ligand conformation changes before and after validation is carried out. The docking method is said to be reliable/valid if the RMSD value is 2 Å, which means the smaller the RMSD value, the closer the position of the natural ligand resulting from the docking to the natural ligand resulting from crystallography. The docking system used in flexible ligand conditions (Muttaqin, 2019).

The validation results with 100 GA runs produced an RMSD value of 1,363 Å, the results can be seen in Figure 3 (C). Thus, the results of the validity evaluation are said to be good because the RMSD value is less than 2 Å (Muttaqin, 2019), so that it can be continued with the next stage, namely docking simulation on the test compound. The simulation parameter values of docking of 15 bioactive compounds of mahogany seeds against target proteins can be seen in the Table 2.

Table 2. Simulation Results Docking

No.	Ligand	Binding Energy (kcal /mol)	Ki (µM)	Electrostatic energy (kcal /mol)
1	Native Ligand	-11.25	5.71	-0.59
2	Glibenclamide	-8.59	505.70	-0.92
3	MSC1	-5.69	67.85	0.01
4	MSC2	-5.16	164.95	-0.03
5	MSC3	-7.52	3.07	0.07
6	MSC4	-6.06	36.31	-0.16
7	MSC5	-5.65	71.64	-0.11
8	MSC6	-8.00	1.36	-0,05
9	MSC7	-7.28	4.58	-0.09
10	MSC8	-8.67	441,96	-0.03
11	MSC9	-6.45	18.76	-0.05
12	MSC10	-6.47	18.12	-0.04
13	MSC11	-7.12	6.01	-0.01
14	MSC12	-8,11	1,13	-0.11
15	MSC13	-6.78	10.67	0.07
16	MSC14	-6.77	10.88	0.01
17	MSC15	-8.86	319,72	-0.16

Note : Mahogany Seed Compound (MSC)

Based on the results of the docking simulation between the receptor and the native ligand, the smallest binding energy value was obtained, in addition, with the docking simulation between the receptor and the native ligand, the coordinate points can be obtained in determining the grid box. Binding energy is a measure of the drug's ability to bind to the receptor. The lower the binding energy value, the better the bond between the drug and the receptor or the higher the ligand bond with its receptor.

However, if the binding energy value is high, the weaker the bond between the ligand and its receptor. The bioactive mahogany seed test compounds that were subjected to docking simulations were 15 compounds, and then the ranking of the 4 best binding energy values was carried out to see the compounds with the best binding or affinity between the ligand and the receptor.

The 4 best compounds were MSC15, SBM8, MSC12, and MSC6, with binding energy values of -8.86 kcal/mol, -8.67 kcal/mol, -8.11 kcal/mol, and -8.00 kcal/mol, respectively. These compounds have binding energy values that are not better when compared to their native ligands, namely with a binding energy value of -11.25 kcal/mol.

While the reference drug that was subjected to docking simulations with the PTP-1B receptor had a binding energy value of -8.59 kcal/mol, the reference drug glibenclamide had a binding energy of -8.59 kcal/mol, which is less favorable than the native ligand (-11.25 kcal/mol), but comparable to several test compounds, particularly MSC15 (-8.86 kcal/mol). This means that there is a good possibility for a stable bond produced by the compound with its receptor. The interactions produced by each compound can be seen in the Figure 3.

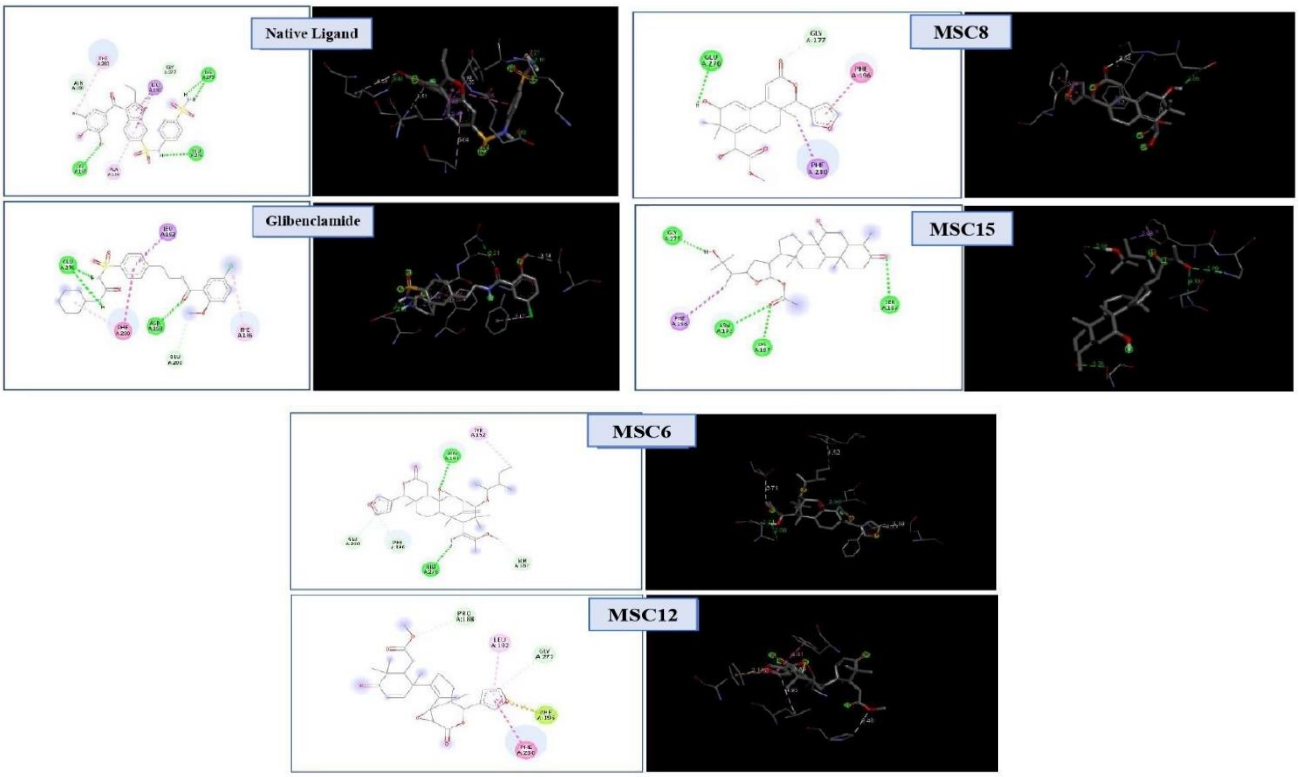

Figure 3. Visualization Results Of The Bond Distances Of The Best Compounds, Native Ligands, And Reference Compounds

In Figure 3, it is known that amino acids interact with the test ligand compound. The image is a visualization of the best compound based on the binding energy it has. In MSC8, MSC15, MSC6, MSC12, the amino acids that are bound are GLU276, GLY277, ASN193, LYS197, SER187, ASN193, GLU276, ASN193. It is known that the amino acid GLU276 binds to 2 compounds, namely MSC15 and MSC6, which are hydrogen bonds. This is similar to previous research on the PTP-1B receptor, namely the presence of hydrogen bonds with amino acid residues GLN-78, ARG-79, and LYS-73 which are catalytic regions in the receptor region (Pujiastuti & Sanjaya, 2017).

In addition, in the native ligand and the reference compound ligand, namely glibenclamide, there is also the amino acid residue GLU276. Thus, there is a similarity of residues between the test

compound and the native ligand and its reference compound. The bond distance of the GLU276 residue in the test ligand is 2.05 Å (MSC8) and 2.98 Å (MSC6). In the native ligand, the GLU276 residue has a bond distance of 1.97 Å., while in the comparison compound, the GLU276 residue has 2 identical bonds with different bond distances of 1.71 Å and 2.02 Å. In addition, the hydrogen bond distance in each compound has varying values. In S15, the hydrogen bond distances are 3.15 Å (ASN193), 2.89 Å (LYS197), 2.08 Å (GLY277) and 3.26 Å (SER187).

Hydrogen bonds can occur between intermolecular and intramolecular, a good hydrogen bond range is at 2.5-3.5 Å (Syahputra *et al*., 2014) or < 3.0 Å (Humaedi *et al*., 2024) thus it can also be seen that several test ligand compounds can bind well. The number of intermolecular hydrogen bonds is very important to note because it can affect the stability of the protein complex (Mascoli *et al*., 2021). Hydrogen bonds can affect the chemical-physical properties of compounds, such as boiling point, melting point, water solubility, chelation ability, and acidity. Changes in these properties can affect the biological activity of compounds (Ruswanto, 2015).

Table 3. Pharmacokinetic Parameter Values Test Ligand Compound

		Absorbtion		Distribution	Metabolism	Excretion
No.	**Compound**	$CaCO_2$ (nM /sec)	HIA (%)	Plasma Protein Binding (%)	CYP3A4 Inhibitor	Clearance (log/min/kg)
1	MSC6	26.24	95.18	85.91	Yes	0,27
2	MSC8	21.33	90.17	86.14	Yes	0,376
3	MSC12	26.63	98.97	92.92	Yes	0,309
4	MSC15	33.50	96.99	89.46	No	-0,027

Note : Mahogany Seed Compound (MSC)

Pharmacokinetics were tested by observing the parameters listed in Table 3, namely CaCO2, Human Intestinal Absorption (HIA), Plasma Protein Bonding, Metabolism (CYP3A4 Inhibitor), and excretion (Clearance) The CaCO2 value can show the ADME of the test ligand compound in the body, the value shows that the test compound has a moderate permeability, which is at a value of 4 – 70 nm/sec where the value predicts that the test ligand compound can penetrate the barrier between intestinal epithelial cells.

Caco-2 cell modeling is recommended as a good in vitro model to predict the absorption of orally administered active substances. The absorption quality of Caco-2 cells is categorized into three groups, namely, <4 low, 4-70 medium, and>70 high The excellent Human Intestinal Absorption (HIA) parameter is in the range of 70-100%, the test ligand compound, in this case, mahogany seeds are included in the range of good HIA % value, showing that this test compound has good absorption power (Annisa Fitriyani Suryana *et al*., 2022).

The absorption values produced by the compounds in table 3 are in the moderate to good range, and HIA gives results >90% for these compounds, strengthening the possibility that these compounds have effective intestinal penetration, because they are in the good range of 70-100%.(Komarudin *et al*., 2021). In terms of distribution, the highest Plasma Protein Binding (PPB) parameter was achieved by MSC12 (92.9%), followed by MSC15 (89.5%), MSC8 (86.1%), and MSC6 (85.9%), which indicates strong plasma binding and the potential for longer circulation times and limited tissue distribution. MSC12 indicates strong plasma binding because it has a value of >90%.(Sagitasa *et al*., 2021). Three compounds, MSC6, MSC8, and MSC12, act as CYP3A4 inhibitors, while MSC15 does not. Inhibiting CYP3A4 can slow the metabolism of other drugs that rely on this pathway, potentially modulating toxicity or therapeutic efficacy. Clinically, CYP3A4 enzyme variability is known to influence drug metabolism by more than 50%, and varies across populations. (Saragih & Muhammad Ichwan, 2025).

In terms of excretion, positive clearance values for MSC6 (0.27 log/min/kg), MSC8 (0.376), and MSC12 (0.309) indicate a relatively rapid elimination rate. In contrast, MSC15 has a negative value (−0.027), which indicates accumulation of the compound in the body or very slow elimination. This is related to bioavailability, and is important for determining the dose level to achieve steady-state concentrations. (Dwi *et al*., 2020)

Table 4. Toxicity Parameter Values Test Ligand Compound

No.	Test Ligand	Toxicity Parameters			
		Hepatotoxicity	Carcinogenicity	Mutagenicity	Citotoxicity
1	MSC6	Inactive	Inactive	Inactive	Inactive
2	MSC8	Inactive	Inactive	Inactive	Inactive
3	MSC12	Inactive	Inactive	Inactive	Inactive
4	MSC15	Inactive	Active	Inactive	Inactive

Note : Mahogany Seed Compound (MSC)

Toxicity prediction through computational methods is not only faster than determining toxic doses in animals, but can also help reduce the number of experiments involving animals. In conducting virtual toxicity tests, the protox web server predicts various toxicity endpoints, including hepatotoxicity, cytotoxicity, carcinogenicity, and cytotoxicity. (Nursanti, 2022)

Based on the toxicity tests conducted, it was found that the MSC15 compound has carcinogenic potential or can cause cancer. All test compounds (MSC6, MSC8, and MSC12) showed inactive properties in all tested toxicity parameters, including hepatotoxicity, carcinogenicity, mutagenicity, and cytotoxicity. However, the MSC15 compound showed differences with active results in the carcinogenicity parameter, while in hepatotoxicity, mutagenicity, and cytotoxicity remained inactive. This indicates that MSC15 has carcinogenic potential that requires attention, although other toxic effects were not detected in this test.

CONCLUSION

Based on in silico molecular docking computational studies, it is known that the bioactive compounds of mahogany seeds have antidiabetic activity by inhibiting the target protein PTP-1B. The mahagonin compound (MSC15) has the best binding energy of -8.86 kcal/mol, this value is better when compared to the comparative ligand glibenclamide which has a binding energy value of -8.59 kcal/mol. The bioactive compounds of mahogany seeds can be further studied through in vitro testin, And pharmacokinetic tests provide good and varied results.

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