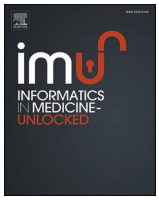
Informatics in Medicine Unlocked 47 (2024) 101517

Contents lists available at ScienceDirect

Informatics in Medicine Unlocked

journal homepage: www.elsevier.com/locate/imu



Self-Nanoemulsifying Drug Delivery System (SNEDDS) formulation and molecular docking of mahogany seed extract (*Swietenia mahagoni*) as anti-hyperglycemic

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ARTICLE INFO

Keywords:
Hyperglycemia
Diabetes mellitus
Mahogany seed extract
Nanoemulsion
Molecular docking

ABSTRACT

Hyperglycemia is one of the causes of diabetes mellitus. One example of a plant used as an anti-hyperglycemic and anti-diabetic herbal medicine is the mahogany plant (*Swietenia mahagoni*). Drugs in nanoemulsion dosages must be developed to increase oral bioavailability and drug solubility from herbal plant extracts. So, research was carried out to determine the formulation and optimization of nanoemulsion from mahogany seed extract (*Swietenia mahagoni*) and its effect on reducing blood glucose levels in mice (*Mus musculus* L.). Based on research that has been carried out, the nanoemulsion formula for mahogany seed extract is characterized by a transmittance percentage of 84.7 % and a particle size of 12.21 nm. Administration of mahogany seed extract and nanoemulsion formulation of mahogany seed extract (*Swietenia mahagoni*) can reduce blood glucose levels in hyperglycemic mice (*Mus musculus* L.). Further, a computational analysis using the molecular docking approach was carried out to analyze the molecular interaction between the main components of mahogany seed (glycidyl oleate and glycidyl palmitoleate) and alpha-glucosidase. The outcome suggested that these substances are bonded to the alpha-glucosidase catalytic sites by hydrogen bonding and hydrophobic interactions and are stable during MD simulation, suggesting that the primary components of mahogany seed may become potential alpha-glucosidase inhibitors to treat diabetes.

1. Introduction

Hyperglycemia is one of the causes of Diabetes Mellitus (DM), a metabolic disease characterized by increased blood glucose levels caused by various factors, including genetic, immunological, environmental, and lifestyle factors [1]. Based on data from the International Diabetes Federation (IDF), in 2007, 425 million people suffered from DM worldwide, and Indonesia was ranked 7th with 107 million people suffering from DM in 2019. The number of DM sufferers in Indonesia continues to increase every year and put Indonesia in 5th place with the most DM sufferers worldwide in 2021. DM sufferers must maintain blood glucose levels under control to avoid complications such as cardiovascular disease, blindness, amputation, and others [2]. To reduce blood glucose levels, DM sufferers generally consume chemical drugs such as glibenclamide, acarbose, and metformin. However, these chemical drugs have side effects such as liver and kidney function disorders, as well as digestive disorders [3].

Plants can produce natural substances or compounds called antinutrients or secondary metabolites [4]. Humans can explore and utilize secondary metabolite compounds in plants in various ways, such as medicinal ingredients in the pharmaceutical industry. These compounds have pharmacological, therapeutic, antioxidant, and antibacterial effects [5]. Using plants as traditional medicinal ingredients was common among Indonesians long before the availability of formal health facilities and the emergence of modern medicine. Medicines made from natural ingredients are considered an alternative for treating disease. One example of a plant used in traditional medicine is the mahogany plant (*Swietenia mahagoni*). Mahogany is a plant from the *Meliaceae* family [6].

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https://doi.org/10.1016/j.imu.2024.101517
Received 22 October 2023; Received in revised form 3 May 2024; Accepted 4 May 2024
Available online 4 May 2024

Mahogany seeds (*Swietenia mahagoni*) have reportedly been used as traditional medicine in Indonesia, Malaysia, India, and several regions in Africa [7]. They are traditionally used as medicines for malaria, hypertension, diabetes, and diarrhea, as antipyretics, and as tonics. The active compounds contained in mahogany seeds have anti-hyperglycemic, anti-diabetic, anti-microbial, anti-inflammatory, hepatoprotective, anti-diarrheal, anti-ulcer, depressant, anti-convulsant, neuropharmacological, anti-HIV, immunomodulatory, insect and larvae repellent, anti-fungal properties. antioxidant, analgesic, platelet aggregation, inhibitor, anti-mutagenic, and anti-cancer [7].

Based on the study results of [7], Mahogany contains phytochemical compounds such as phospholipids, alkaloids, phenols, flavonoids, anthraquinones, saponins, terpenoids, cardiac glycosides, essential oils, and long-chain unsaturated acids. The phytochemical contents isolated from seeds, bark, twigs, leaves, and stems of mahogany are limonoid compounds (81.91 %), polyphenols (4.26 %), steroids (4.26 %), essential oils (6.38 %), fatty acids (1.06 %), coumarins (1.06 %) and lignans (1.06 %).

Herbal medicines are generally packaged in an oral dosage form; this is because administering medicines orally is the method that is considered the safest, most comfortable, and cheapest. However, the low solubility and poor oral bioavailability of herbal plant extracts mean the drug's effectiveness in the body is less than optimal. Therefore, it is necessary to develop oil-based drug formulations in nanoemulsions, which are expected to increase the oral bioavailability and solubility of drugs from herbal plant extracts. Nanoemulsion is a stable and transparent dosage form; it has a minimal droplet size, usually 20–200 nm [8]. Nanoemulsions are made in a drug delivery system called the Self-Nanoemulsifying Drug Delivery System (SNEDDS). SNEDDS is a mixture of oil, surfactant, cosurfactant, and active substances that, when mixed with water, form an oil/water (O/W) type nanoemulsion [9].

Based on the above description, we conducted this research to determine the formulation and optimization of a nanoemulsion from mahogany seed extract (*Swietenia mahagoni*) and its effect on reducing blood glucose levels in mice (*Mus musculus* L.). This research has never been carried out to make mahogany seed extract in nanoemulsion form and test its activity on blood sugar levels in mice.

2. Methods

2.1. Apparatus and materials

The apparatus used in this research were glassware, blender, analytical balance, 1 set of soxhlet extraction tools, rotary evaporator, oven, GC-MS instrument, sample bottles and vials, centrifugation, particle size analyzer (PSA), magnetic stirrer, sonicator, spectrophotometer, hot plate, syringe, and oral sonde. The materials used in this research were mahogany seeds (*Swietenia mahagoni*), ethyl acetate, distilled water, filter paper, aqua deion, alloxan, glibenclamide, tween 80, PEG 400, aluminum foil, male mice (*Mus musculus* L.), Na -CMC, and 5 % glucose solution.

2.2. Sample preparation and extraction

Dried Mahogany seeds are chopped and then ground using a blender. 50 g of mahogany seed simplicia were then extracted using the soxhletation method using 500 mL of ethyl acetate solvent. The extraction process was carried out for 6 h at a temperature of 65 °C. The filtrate was then evaporated using a rotary evaporator at 40 °C to remove the solvent. The evaporated extract is placed in an oven at 40 °C to ensure the solvent has evaporated completely. The extract obtained is then weighed to calculate the % yield. % yield is calculated using the following formula.

$$\%\ \text{Reaction Yield} = \frac{\text{extract weight}}{\text{Dry weight of simplicia}} \times 100\%$$

The results of the mahogany seed extract were then subjected to a GC-MS test to determine the extract's active compound content.

2.3. GC-MS analysis

GC-MS analysis of fatty acid methyl esters (FAMEs) was performed using an Agilent 1909Is-433. An HP-5MS (5 % phenyl methylsiloxane) capillary column with dimensions of 30 m × 0.25 mm inner diameter x 0.25 μm film thickness (Agilent Technologies, Palo Alto, CA, USA) was used for the separation of fatty acid methyl esters. The initial temperature at 150 °C was set for 2 min before being increased to 230°C at a rate of 4 °C/min, and then set at 230°C for 5 min. The separation ratio was 1:50; helium was used as the carrier gas, with a flow rate of 0.8 mL/min. Injection temperatures are 240°C and 260°C. Mass Spectrometry was set in electrons at 70 eV in the 50–550 *m/z* range.

2.4. Nanoemulsion formulation

The nanoemulsion formulation's determination was based on previous preliminary studies' results. Nanoemulsion is made by mixing the ratio of mahogany seed extract: surfactant (tween 80): cosurfactant PEG 400 in a 1: 7: 1 ratio. The formula sample is put into a 20 mL vial. The sample was then homogenized using a magnetic stirrer (100 rpm) for 2 h and placed in a sonicator for 1 h. The mixture was then added with aqua deion in a ratio of 1:5 and then stirred again until homogeneous. After that, an evaluation test of the nanoemulsion preparation was carried out.

2.5. Nanoemulsion evaluation test

a. Physical Stability Test

The physical stability of the nanoemulsion was tested using a centrifugation test at a speed of 12,000 rpm for 15 min. Then, phase separation was observed. A stable nanoemulsion can be observed with no separation of the two phases.

b. Test Percent Transmittance (%)

The nanoemulsion preparation was put into a cuvette, and the percent transmittance at a wavelength of 650 nm was measured using a UV–Vis spectrophotometer. Aqua Deion was used as a blank during testing. A formulation with a 90%–100 % transmittance percentage indicates a clear and transparent visual appearance.

c .Zeta Potential and Particle Size Test

Zeta potential and particle size tests were performed using an electrophoretic light scattering model (Delsa Nano C Particle Analyner, Becman Coulter). A total of 1 g of a mixture of oil, surfactant, and cosurfactant was dispersed in 5 mL of aqua deion and measured. Zeta potential was determined using electrophoretic light scattering mode (Delsa^{TM}Nano C Particle Analyzer, Beckman Coulter). A total of 1 g of a mixture of oil, surfactant, and cosurfactant was dispersed in 5 mL of aqua deion and measured. The nanoemulsion particle size and polydispersity index were determined using photon correlation spectroscopy mode (Delsa^{TM}Nano C Particle Analyzer, Beckman Coulter).

2.6. Making test materials

a. 1 % Na-CMC Solution

Two grams of Na-CMC were dissolved in 150 mL of distilled water

and then heated on a hot plate while stirring. After homogenization, distilled water was added until the total volume was 200 mL.

b. Glibenclamide Solution

1 mg of glibenclamide was dissolved in 25 mL of 1 % Na-CMC solution.

c. Alloxan Solution

1 mg of alloxan was dissolved in 100 mL of 1 % Na-CMC solution.

d. Mahogany Seed Extract Solution

The mahogany seed extract was weighed at 150 mg and then suspended in 1 % Na-CMC solution for 10 mL.

e. Mahogany Seed Extract Nanoemulsion Formulation Solution

A total of 1 mL of mahogany seed extract nanoemulsion preparation was mixed with 5 mL of aqua deion and stirred until homogeneous.

2.7. Test for reducing blood glucose levels in mice

Experimental animals used in this study were 24 male mice (*Mus musculus* L.), which had been induced by alloxan to achieve a state of hyperglycemia. All mice were divided into 4 groups, each consisting of 6 mice with different treatments in each group. Before testing, mice were acclimatized for 6 days. During the acclimatization and experimental periods, mice were given AD2 food and water ad libitum.

After acclimatization, on day 7, the mice were fasted for 8 h before measuring initial blood glucose levels (H0). Blood collection was carried out by cutting the lateral vein of the tail of the mouse. Blood glucose is then measured using a glucometer. On day 8, mice were induced with alloxan orally at a 150 mg/kgBW dose. Next, the mice were given a 5 % glucose solution for 3 days to accelerate the hyperglycemia state. On the 11th day, the mice's blood glucose levels were measured after administering alloxan (H1).

The hyperglycemic mice were then divided into 4 groups, and each group consisted of 6 mice; each group would receive a different treatment, namely group 1 as a negative control treatment group without any treatment for 7 days. Group 2, as a positive control treatment group, was given glibenclamide 1 mg/kgBW orally for 7 days. Group 3, as treatment group 1, was given 150 mg/kgBB mahogany seed extract orally for 7 days. Group 4, as treatment group 2, was given a nanoemulsion preparation of mahogany seed extract 150 mg/kgBW orally for 7 days. On the 19th day, the mice's final blood glucose levels (H2) were measured. The percentage reduction in blood glucose levels is calculated using the following formula:

$$\%\ \mathrm{DBG} = \frac{\mathrm{H1} - \mathrm{H2}}{\mathrm{H1}} \times 100\%$$

DBG: Decreased Blood Glucose.

H1. Average blood glucose levels before treatment.

H2. Average blood glucose levels after treatment.

2.8. Data analysis

The percentage reduction in blood glucose levels of mice obtained was analyzed using SPSS 28 software using the One-Way ANOVA statistical test. If there is a significant difference, continue with the Post Hoc Tukey test at a confidence level of 95 % ($p < 0.05$).

3. Results and discussion

3.1. Results of mahogany seed extract yield

Mahogany seeds (*Swietenia mahagoni*) were extracted with ethyl acetate solvent using the soxhletation method. Based on the % yield calculation results, data on the yield of mahogany seed extract was obtained, which can be seen in Fig. 1.

It is known that from 311,699 g of mahogany seed simplicia extracted, 102,432 g of mahogany seed extract was obtained with a % extract yield value of 32.86 %. This shows that the extract obtained can be said to be good and has high active compounds. If the yield of the resulting extract is greater, the number of active compounds contained in the sample will also be higher [10].

3.2. GC-MS results of mahogany seed extract

The identification of mahogany seed extract using a GC-MS instrument aims to analyze the mixed compounds contained in the extract. The chromatogram in Fig. 2 shows 208 peaks, meaning about 208 compounds are present in the mahogany seed extract. Then, the mass spectrum data of the compound were compared with the database in the NIST library. The screening process is based on the total concentration of each compound due to the quantity of compounds indicated to be an essential factor for enhancing bioactivity.

Based on the results of GC-MS analysis of mahogany seed extract, the peak that appeared at the retention time from 26,920 min to 26,968 min indicated the most dominant compound content in the sample. The main compounds detected in mahogany seed extract were 9-Octadecenoic acid (Z)-, oxiranylmethyl ester, Glycidyl palmitoleate, Glycidyl (Z)-9-Heptadecenoate, 9,12,15-Octadecatrienoic acid, 2,3 dihydroxypropyl ester, 9,12,15-Octadecatrienoic acid, 2-phenyl-1,3-dioxan-5-yl ester, 1-Heptatriacotanol. The GC-MS test results of mahogany seed ethanol extract can be seen in Table 1.

Based on the results of the GC-MS analysis, 6 main compounds, or the most dominant compounds, are contained in the mahogany seed extract sample. All these compounds have biological activity that can influence lowering blood sugar. According to Ref. [11], the compound 9,19-Cyclolanostan-3-ol, 24,24-epoxymethano-, acetate has antioxidant and antimicrobial activity. Glycidyl palmitoleate and Glycidyl (Z)-9-Heptadecenoate compounds are known to have antibacterial activity [12]. The compound 9,12-Octadecadienoic acid, (2-phenyl-1, 3-dioAlpha-glucosidaselan-4-yl)methyl ester and the compound 9-Octadecenoic acid (Z)-, oxiranylmethyl ester have antioxidant, anti-inflammatory and antimicrobial activity [13]. Meanwhile, the compound 1-Heptatriacotanol is reported to have antioxidant, anticancer, and anti-inflammatory activity [14].

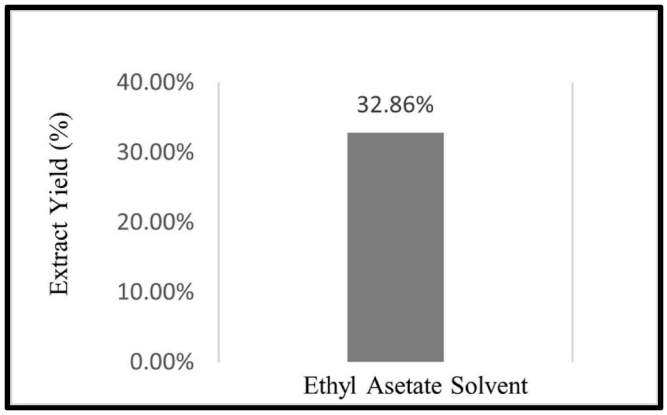

Fig. 1. % yield of mahogany seed extract.

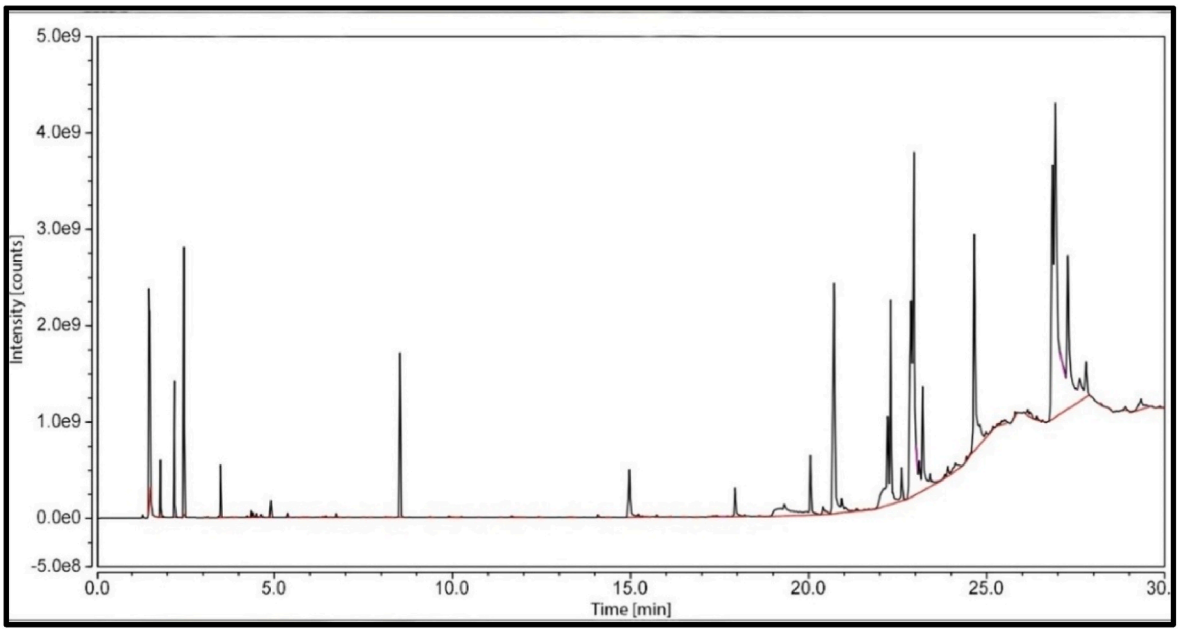

Fig. 2. The GC-MS chromatogram of a mahogany seed extract (*Swietenia mahagoni*).

Table 1
GC-MS results of mahogany seed extract.

Retention Time	% Area	Chemical Components	Mw (g/mol)
26.920	9.11	Glycidyl oleate	265
26.920	9.11	Glycidyl palmitoleate	129
26.920	9.11	Glycidyl (Z)-9-Heptadecenoate	129
26.968	8.61	9,12,15-Octadecatrienoic acid, 2,3-dihydroxypropyl ester,	155
26.968	8.61	9,12,15-Octadecatrienoic acid, 2-phenyl-1,3-dioxan-5-yl ester	334
26.968	8.61	1-Heptatriacotanol	190

3.3. Nanoemulsion evaluation test results

Nanoemulsion is a drug delivery system consisting of water and oil phases stabilized by a combination of surfactant and cosurfactant with an average droplet size of <100 nm [15]. Surfactants and cosurfactants are essential components in nanoemulsion formulations. According to Ref. [16], surfactants reduce the interfacial tension between two immiscible liquids due to the presence of hydrophilic groups at the head and hydrophobic groups at the tail. Two types of surfactants are used, namely Cremophor RH 40 and Tween 80; both are non-ionic surfactants, so they will not irritate the skin when used. Cosurfactants play a role in helping the solubility of solutes in the dispersion medium by increasing the flexibility of the layer around the droplet area and reducing surface free energy so that stability can be maintained. In addition, by using cosurfactants, the concentration of surfactant used can be reduced, thereby reducing the risk of irritation. The cosurfactant used in the formula is PEG 400. The oil phase in the nanoemulsion acts as a carrier that can dissolve hydrophobic active substances. The oil phase used is mahogany seed extract.

Nanoemulsions can form spontaneously or non-spontaneously, depending on the energy provided during the manufacturing process. This research combines these two methods because the oil phase and water phase are mixed slowly using a magnetic stirrer and then assisted by the sonication method, which uses ultrasonic waves to convert electrical energy into physical vibrations, reducing particle size to 0.2 μm. The mahogany seed extract nanoemulsion evaluation tests included the nanoemulsion stability test, percent transmittance test (%), zeta potential test, and particle size test.

The best formula is selected based on visual appearance and percent transmittance value. Percent transmittance shows the level of clarity of a liquid preparation expressed in percent form. A good nanoemulsion has an apparent visual appearance and a transmittance percentage of 90–100 % or close to the transmittance percentage of water, namely 100 %. The greater the transmittance value or the clearer the nanoemulsion, it can be estimated that the nanoemulsion droplets have reached nanometer size. The size of the dispersed phase dramatically influences the appearance of the nanoemulsion. Suppose the nanoemulsion system has a minimal globule size through which light passes. In that case, the light beam will be transmitted so that the color of the solution looks transparent, and the resulting transmittance is more excellent. Aqua deion is used as a comparison because it does not have particles that block light transmission, so it will transmit light that passes through it without any light scattering effects, so it has a transmittance value of 100 % [16].

The mahogany seed extract nanoemulsion evaluation test results show that the SNEEDS formula has nanoemulsion criteria because the percent transmittance value obtained is close to 100 %, and the particle size value is 12.21 nm. The mahogany seed extract nanoemulsion evaluation test results can be seen in Table 2.

3.4. Test results for reducing blood glucose levels in mice

In this study, 24 male mice were divided into 4 groups, with 6 mice for each group. The first group was the negative control group, and mice were not given any treatment. This group was used to see and ensure that the blood glucose-lowering activity test method was correct. The next group was the positive control group. Diabetic mice were treated with glibenclamide at a dose of 1 mg/kgBW; this group was used to show the effect of reducing mice's blood sugar in the study. Next, treatment

Table 2
Evaluation test results of mahogany seed extract nanoemulsion.

Formulation	Physical Stability	Percent Transmittance (%)	Particle Size (nm)
P2	There is no phase separation	84,7 %	12,21

group 1 was given a suspension of mahogany seed extract at 150 mg/KgBW. Next, treatment group 2 was given a mahogany seed extract nanoemulsion formulation at 150 mg/KgBW.

The activity of the mahogany seed extract nanoemulsion formula was then tested to reduce the blood glucose levels of mice, as shown in Table 3 and Fig. 3.

The results of the One-Way ANOVA test show a significance value of less than 0.05 ($p < 0.05$), namely 0.001. This means that administering extracts and nanoemulsion formulations from mahogany seed extract significantly reduce blood glucose levels in mice, and there are differences in the effects between treatments. Based on the results of the Post Hoc Tukey test, The average percentage reduction in blood glucose levels of mice in the negative control treatment group was significantly different from the positive control treatment group and the treatment group given extracts and nanoemulsion formulations from mahogany seed extract. Meanwhile, the positive control treatment group was not significantly different from the treatment group given the extract and nanoemulsion formulation from mahogany seed extract.

Based on the research results, administering extract treatment and nanoemulsion formulation from mahogany seed extract can reduce blood glucose levels in hyperglycemic mice. This is in line with the research results of [17], that mahogany seed extract has the activity of reducing blood glucose levels in white mice (*Mus Musculus* L.) at a dose of 50mg/kgBB mice. Other researchers also reported that giving dry mahogany seed extract to diabetic mice at 10 mg/20g BW), 20 mg/20g BW, and 40 mg/20g BW could reduce random blood sugar levels in male Wistar rats [18].

It has been reported that mahogany seed extract can increase insulin production and stimulate the regeneration of pancreatic β cells [19]. Seed extract is also reported to activate the glucokinase enzyme in lowering blood glucose levels and has hypoglycemic activity in type 2 diabetic rats. According to Ref. [19], Mahogany seed extract contains phytochemical compounds such as alia, flavonoids, swietenine, saponins and tannins, which are hypoglycemic and antidiabetic antioxidants. Flavonoids are antidiabetic agents because they protect against β-cell damage, increased β-cell proliferation, and preservation of insulin signaling by increasing insulin secretion.

According to Ref. [6], the compound that is thought to play a significant role in the antidiabetic activity of mahogany seeds is swietenin. Swietenin is a class of tetranortriterpenoid compounds, a natural PPAR (Peroxisome Proliferator-Activated Receptor) agonist. It has a working mechanism of activating insulin-responsive genes, which can stimulate insulin to form and translocate GLUT (Glucose Transporter) to cell membranes in peripheral organs so that peripheral glucose absorption and use increase.

Table 3
Average blood sugar levels (mg/dL) of male mice (*Mus musculus* L.) before and after treatment.

Treatment	Blood Sugar (mg/dL)			Decreased Blood Sugar Levels After Treatment (mg/dl)(H1-H2)	Percentage Reduction in Blood Sugar Levels (%)
	H0	H1	H2		
K-	76.00	77.00	99.33	−22.33	$-29.00 \pm 7,91^{a}$
K+	95,00	215,00	115,33	99,67	$61,41 \pm 11,39^{b}$
P1	55,00	170,67	121	49,67	$29,10 \pm 7,17^{b}$
P2	82,00	204,67	91,33	113,34	$55,38 \pm 20,17^{b}$

Notes: values (mean ± standard deviation) followed by different superscript letters in the same column indicate significant differences ($P < 0.05$). K-; negative control group without any treatment, K+; positive control group was given glibenclamide 1 mg/kgBW orally, P1; treatment group 1 was given mahogany seed extract 150 mg/kgBW orally, P2; treatment group 2 was given mahogany seed extract nanoemulsion formula 150 mg/kgBW orally, H0; initial blood glucose levels of mice (day 8), H2; blood glucose levels of mice after alloxan induction (day 12), and H2; blood glucose levels of mice after treatment (19th day).

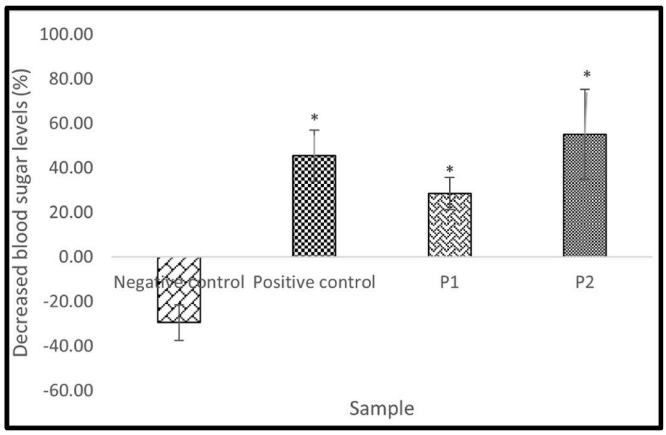

Fig. 3. Percentage reduction in blood sugar levels of mahogany seed nanoemulsion formulation.

3.5. Docking study

To gain insight into the molecular interactions between potential drug candidates (ligands) and target proteins (receptors), Mahogany Seed active compounds (tested ligands) were utilized to test the pharmacological activity as an anti-hyperglycemic using molecular docking [20–22]. The 3D structure of the glycidyl oleate (PubChem ID: 5354568) and glycidyl palmitoleate (PubChem ID: 23624909) were retrieved from the PubChem database. The SDF format was downloaded and saved for the docking procedure. AutoDock Vina is a widely used docking tool for molecular docking studies. To run the simulation, the ligand and receptor molecules are prepared. For the ligand molecules, the SDF formats were converted to PDB format using Open Babel 2.4.1 program packages [23]. Hydrogen atoms and charges (Kollman's united atomic charges) were computed to the ligand using AutoDock Tools 1.5.6 [24]. The rotatable bond for the ligand was set as the software's default. Then, the tested ligands were saved to PDBQT format. For the receptor preparation, the crystal structure of alpha-glucosidase was taken from the protein database (PDB: 3w37) as shown in Fig. 4 [25]. Hydrogen atoms and charges were also added to the receptor. The Auto Dock Tools 1.5.6 program converts receptor extension *.pdb to *.pdbqt. A grid box size is

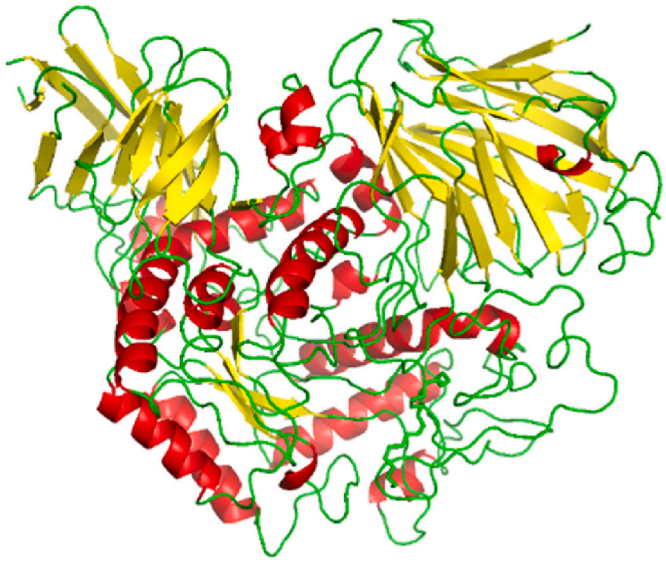

Fig. 4. A carton model presents the 3D structure of Alpha-glucosidase. The red, yellow, and green colors refer to the alpha-helix, beta-sheet, and turn. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

set at X = 4.961, Y = −5.498, Z = −22.257 with a grid spacing of 1 Å (Å), and the calculated number of point dimensions was 22, 20, and 20 Å. The Broyden-Fletcher-Goldfarb-Shanno (BFGS) method was then used to search for stable structures of the ligands once they bind in the protein binding pocket region. All other docking criteria are set to AutoDock Vina's default values. By employing the PLIP program (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index) gathered with PyMOL software, the simulated results from docking were visualized in 3D model. The docking protocols were calculated following our earlier research, as provided in Refs. [26–28].

An advanced experimental investigation using X-ray analysis is needed to learn more about the molecular interaction of the Mahogany Seed active compounds with a target protein as anti-hyperglycemic. However, experimental investigation needs more effort and time to understand the molecular phenomena of Mahogany Seed substances acting on a protein target. To handle this issue, computational research utilizing the molecular docking approach can be applied to examine the structural and conformational shifts of the ligand-receptor complex. Also, this method is used to determine the physical and chemical views of the binding activity of mahogany seed into the moiety of alpha-glucosidase. Preparing the protein target (receptor) and potential medications (ligand) is necessary. Regarding receptor molecules, the crystal structure of alpha-glucosidase obtained from the protein database (PDB: 3w37) [25] was selected for docking due to its activity in increasing the glucose molecules in the cell. The ligand molecules were made from the extracted mahogany seed using GC-MS analysis. The binding energies and the binding posture between the ligands and receptors were determined from our docking simulations and are shown in Table 4 and Fig. 5, respectively. Tables 5 and 6 also gave information on the hydrogen bonds and hydrophobic interactions between the ligand/receptor complexes.

In this study, only the main components of mahogany seed, such as glycidyl oleate and glycidyl, were chosen as the ligand molecules. Acarbose, on the other hand, is employed as a Control because it can suppress alpha-glucosidase activity. A negative value for the ligand-receptor complex's binding energy indicates the ligand's potential to bind to the receptor site. Two complexes, including the control, showed varied negative binding energies, as shown in Table 4, indicating the ligands can form a complex formation with the Alpha-glucosidase enzyme. Two active compounds showed negative values binding energy, which are −5.9 kcal/mol and −6.0 kcal/mol for Glycidyl oleate and Glycidyl, indicating that the ligands could bind to the receptor, forming a ligan-receptor complex. In addition, the ligands of all complexes do not have significant scores of binding energy with Acarbose (a positive control), with a binding energy of −6.9 kcal/mol. This finding revealed that those 2 ligands found in the extract of *Mahogany Seed* probably hold the potential as inhibitors for Alpha-glucosidase. Thus, to identify the molecular interactions, including hydrogen bond and hydrophobic interaction between ligand and receptor, the snapshot structure of those ligands was analyzed using PLIP server and LigPlot v.4.5.3 program packages.

Fig. 5 shows the geometrical pocket and binding site of the ligands in combination with the receptor. Table 5 provides a list of all complexes' specific hydrogen bonds. It was discovered that Glycidyl oleate engaged in hydrogen bonding with receptor residue SER497. In Glycidyl Palmitoleate, the ASP232 and SER497 residues formed hydrogen bonds. Hydrogen bonds were created with ASP232, ASN496, SER497, and SER505 residues for acarbose (a Control).

On the other hand, Table 6 shows the hydrophobic interactions between ligand and receptor. The hydrophobic contact between glycidyl oleate and the receptor's ALA231, ASP9232, TRP432, PHE476, and LYS506 residues was created. Hydrophobic contact was demonstrated when Glycidyl Palmitoleate interacted with receptor residues TRP432, PHE476, and LYS506. In contrast, the hydrophobic contact between the ligand and residue LYS506 was seen as a control. Since these findings govern the hydrogen bonds between the ligand and receptor, all primary ligands in the collected Mahogany Seed substances may develop into stable complexes. Additionally, the molecules of glycidyl oleate and 2 glycidyl palmitoleate attached to the identical Acarbose residues suggested that those compounds share a similar level of alpha-glucosidase inhibitory action. In addition, the catalytic site of Alpha-glucosidase, consisting of residues ASP232, TRP329, ILE358, ARG552, HIS626, ASP469, TRP467, ASP568, ALA234, PHE601, MET470, and ILE233, is a crucial target for inhibiting Alpha-glucosidase [25]. Therefore, it is hypothesized that the ligand that can bind to one of these residues can potentially be a medication for treating diabetes. As a result of our simulations, each ligand is bonded to those residues by hydrogen bonds and hydrophobic interactions, and these substances may become alpha-glucosidase inhibitors.

Table 4
The binding energy of ligands in complex with receptors is obtained by molecular docking.

Complex	Compound	Binding Energy (kcal/mol)
1	Glycidyl oleate	−5.9
2	Glycidyl Palmitoleate	−6.0
3	Acarbose (Control)	−6.9

3.6. All-atom MD simulation

The Amber20 packages were used to perform an all-atom MD simulation to evaluate the stability of the ligand in its interaction with the receptor [29]. The system's cubic box size takes TIP3P water models into account [30]. The force fields GAFF and AMBER14 were used to determine the characteristics of force fields for proteins and ligands [31]. The Particle Mesh Ewald (PME) algorithm [32] was used to produce the electrostatic interactions and the SHAKE algorithm [33] was employed to restrict the distance between the hydrogen atoms. The switching cutoff distance was calculated to be 10 A. The time step used in each simulation was 2 fs. The MD simulation was initiated by lowering system energy overall. We then used the NVT ensemble to raise the temperature over 2000 ps stepwise from 0 to 300 K. Temperature and pressure in the system were maintained at 300 K and 1 atm, respectively, using the Langevin thermostat [34] and the isotropic position scaling method. An NPT ensemble was then used to execute an MD simulation for 100 ns. The trajectory was captured at 10 ps, or 5000 steps. The MD-simulated trajectories were then examined using the CPPTRAJ program [21,35]. The all-atom MD simulation protocol steps were presented in more detail in our previous studies [36,37].

A molecular dynamics simulation is performed to confirm the stability of the protein/ligand complexes found using docking simulation. The simulation used four steps: equilibration, production run, heating process, and minimization. As seen in Fig. 6, the resulting MD trajectories were used to estimate the validation metrics. MD simulation was carried out using three complexes: glycidyl oleate (Model 1), glycidyl palmitoleate (Model 2), and acarbose (Control). The RMSD value for each complex is displayed in Fig. 6(a). Three complexes, i.e., model 1, model 2, and control, involve a slight fluctuation in the range of 0–5 ns; beyond this point, the RMSD is expected to remain constant until the simulation is finished. Furthermore, we found that the ligand in model 2 has a smaller RMSD than the ligands in the other models and even the controls, suggesting that the ligand can connect to the protein's active site more efficiently and create a more stable complex. Despite minor oscillations, all models, taken together, reached the equilibrium phase during the simulation because of the interactions between the atoms in the system, hydrophobic interaction, hydrogen bonding, electrostatic interaction, etc. The protein-ligand structure may fluctuate throughout the MD simulation.

The RMSF profile in Fig. 6(b) implied that amino acid residues were flexible for all complexes during the simulation. The visual trend shows that models 1, 2, and control tend to a more flexible shape, suggesting

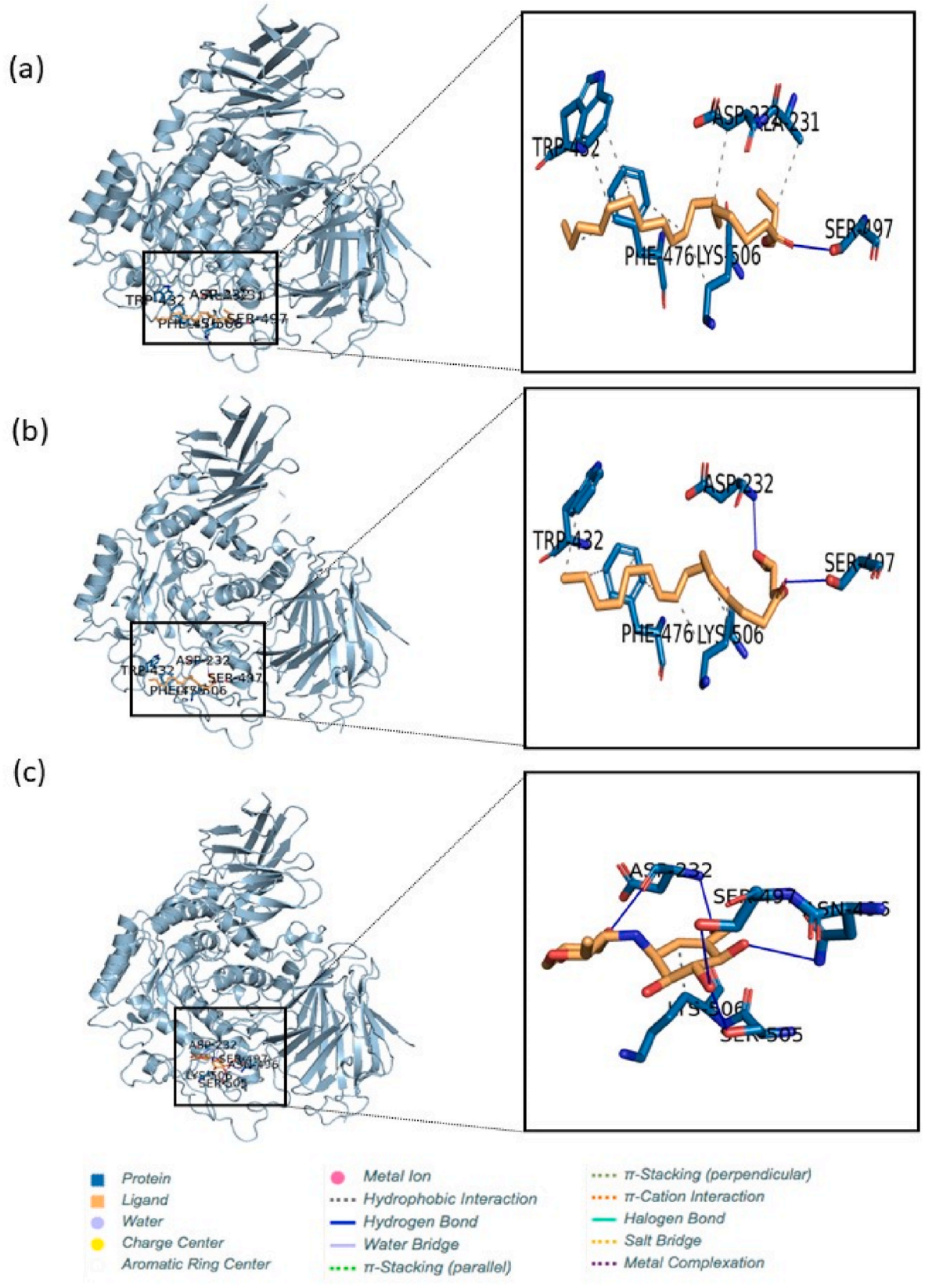

Fig. 5. The binding poses between ligand and receptor obtained by molecular docking.

Table 5
Hydrogen bonds of ligands in complex with receptor.

Compound	Residues	AA	Distance H-A	Distance D-A	Donor Angle	Donor Atom	Acceptor Atom
Glycidyl oleate	497A	SER	2.23	2.86	122.78	4386 [O3]	8242 [O2]
Glycidyl Palmitoleate	232A	ASP	2.24	2.98	128.34	1712 [Nam]	8237 [O3]
	497A	SER	2.18	2.82	123.53	4386 [O3]	8243 [O2]
Acarbose (Control)	232A	ASP	2.36	2.82	108.97	8241 [O3]	1716 [O2]
	232A	ASP	2.03	3.03	165.62	1712 [Nam]	8257 [O3]
	496A	ASN	2.77	3.45	124.3	4371 [Nam]	8251 [O3]
	497A	SER	3.21	3.91	132.06	4386 [O3]	8253 [O3]
	497A	SER	3.62	3.91	100.66	8253 [O3]	4386 [O3]
	505A	SER	2.37	3.11	134.23	4457 [O3]	8253 [O3]

Table 6
Hydrophobic interaction of ligands in complex with receptor.

Compound	Residue	AA	Distance	Ligand Atom	Protein Atom
Glycidyl oleate	231A	ALA	3.94	8239	1711
	232A	ASP	3.77	8248	1717
	432A	TRP	3.41	8255	3751
	432A	TRP	3.87	8254	3752
	476A	PHE	3.93	8258	4192
	476A	PHE	3.47	8256	4194
	476A	PHE	3.88	8254	4195
	476A	PHE	3.51	8250	4191
	506A	LYS	3.55	8250	4466
Glycidyl Palmitoleate	432A	TRP	3.66	8258	3751
	476A	PHE	3.91	8257	4194
	476A	PHE	3.59	8256	4192
	476A	PHE	3.75	8255	4190
	476A	PHE	3.68	8254	4193
	476A	PHE	3.62	8252	4191
	506A	LYS	3.63	8251	4466
	506A	LYS	3.76	8249	4464
	506A	LYS	3.59	8246	4465
Acarbose (Control)	506A	LYS	3.41	8248	4464

that the ligand can attach to the receptor due to the flexibility of the complex. In Fig. 6(c), we showed the radius of gyration (Rg) for every complex. The RG value is connected to the packaging system. Our results showed that, except for a minor fluctuation throughout the MD simulation, the complexes had a more compact structure and that the radius of gyration for each complex did not change much. Furthermore, the 370–470 hydrogen bond area in Fig. 6(d) suggests that these interactions were critical to preserving a stable receptor-ligand complex during the MD simulation.

The binding energy obtained by molecular docking shown in Table 4 demonstrated no significant energy contribution between the tested ligands (glycidyl oleate and glycidyl palmitoleate) and the control. Therefore, it is difficult to determine which compounds occupy the most stable complex formation with the receptor (alpha-glucosidase). Also, in docking instruments, no solvent effect or event physical properties such as temperature and pressure parameters are involved in estimating the binding energies. The MM-GBSA method was employed to calculate the binding energies of all complexes in the TIP3P solvent system to handle this issue. The equilibrium state from 75 to 100 ns (2,500 frames) was used to calculate the binding energy of each complex. The binding energy, including the several energy contributions for each complex, was listed in Table 7. The binding energies of models 1 and 2 are −29.79 kcal/mol and −57.90 kcal/mol, respectively. Meanwhile, the binding energy of the control was found to be −21.90 kcal/mol. These results revealed that two complexes had higher binding energies than the control, denoting that the ligands of each complex might have strong binding to the catalytic site of alpha-glucosidase. Further, this finding demonstrated that those two ligands were more stable structures than the control based on the binding energy score. Hence, they might become potential inhibitors for alpha-glucosidase in treating hypertension. Besides, we saw that the E_{vdw}, $E_{ele,}$ and E_{GB} contributions are significantly different, which might affect the variation of the binding energy score of each complex.

3.7. ADMET and Toxicology analysis

Since toxicity is a crucial consideration for administering candidate medications, it is necessary to analyze the toxicological features of the targeted compounds to identify promising drugs from those compounds. Toxicological characteristics such as respiratory toxicity, reproductive toxicity, nephrotoxicity, skin sensitization, and carcinogens were predicted using the AdmetSAR server. Table 8 demonstrates that every single main component in mahogany seed passed the chosen toxicological standards. Conversely, Lipinski's rule of five and Veber's rule were also used to analyze the pharmacokinetic features concerning the ADME (absorption, distribution, metabolism, and excretion) of all main substances. A chemical is said to exhibit optimal drug-likeness behavior if it meets four out of the five requirements, which are: molecular weight less than 500 Da; lipophilicity less than five; ≤5 hydrogen bond donors; ≤10 hydrogen bond acceptor; and molar refractivity between 40 and 130 [38]. SwissADME is an online tool that was used to identify all those qualities, which are mentioned in Table 9. The tested compounds (Glycidyl oleate and Glycidyl Palmitoleat), including the control (Acarbose), satisfy Veber's and Lipinski's rule of five. These findings indicated that those substances could be excellent candidates for drugs, so they were saved for further examination.

4. Conclusion

Based on research that has been carried out, the nanoemulsion formula for mahogany seed extract has characteristics of a transmittance percentage of 84.7 % and a particle size of 12.21 nm. Administration of mahogany seed extract and nanoemulsion formulation of mahogany seed extract (*Swietenia mahagoni*) can reduce blood glucose levels in hyperglycemic mice (*Mus musculus* L.). Additionally, computational research was done to understand the molecular interactions of the main components of mahogany seed, such as glycidyl oleate and glycidyl Palmitoleate with alpha-glucosidase, using molecular docking and MD simulation. Our research showed that these substances were bonded to the catalytic sites of alpha-glucosidase by hydrogen bonds and hydrophobic interactions, indicating that these significant components of mahogany seed have pharmacological effects that block alpha-glucosidase activity. Further, those two models are stable along MD simulation, suggesting the tested compounds may become potential drug candidates for diabetes treatment.

Ethical statement for solid state ionics

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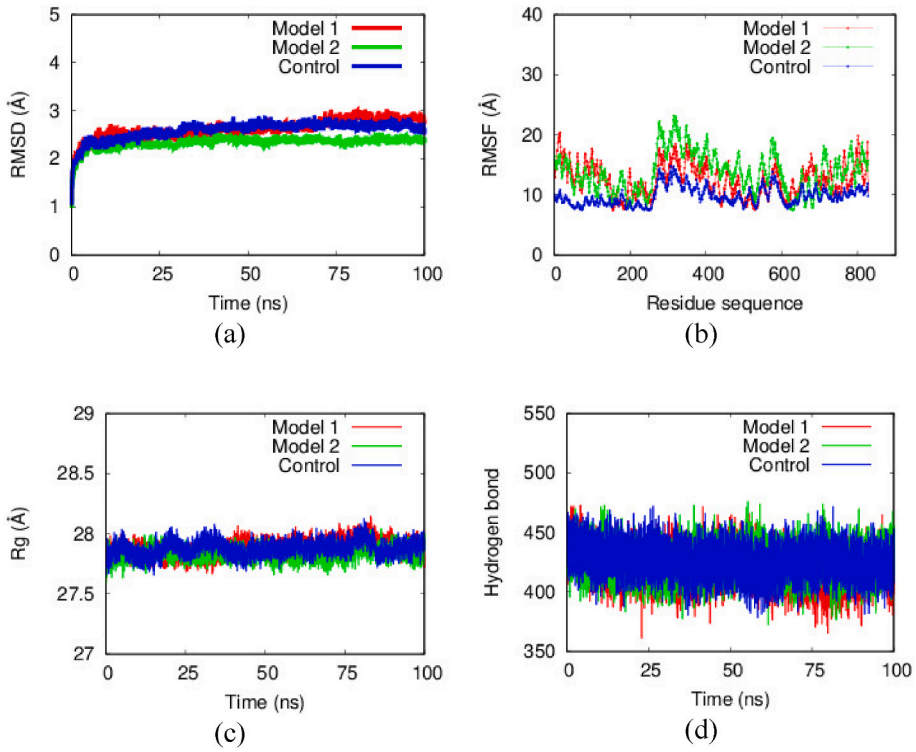

Fig. 6. The MD validation metrics consisted of (a) the RMSD value of the complexes, (b) the RMSF descriptor, (c) the Radius of gyration (Rg), and (d) Hydrogen bonds. Red, green, and blue colors denoted model1, model2 and control, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 7
shows each energy term's portion of the binding energy for every model. The energy contributions were displayed in kcal/mol. The standard deviation is in parentheses.

Model	E_{vdw}	E_{ele}	E_{GB}	E_{SA}	ΔG_{MM}	ΔG_{GBSA}	ΔG_{bind}
Model 1	−32.20 (4.36)	−0.17 (1.29)	7.13 (1.83)	−4.28 (0.40)	−32.38 (4.60)	2.85 (1.75)	−29.53 (3.90)
Model 2	−61.77 (2.96)	−4.48 (2.97)	15.32 (2.87)	−6.97 (0.27)	−66.25 (4.62)	8.35 (2.82)	−57.9 (3.06)
Control	−39.80 (2.01)	−11.00 (2.50)	33.22 (2.42)	−4.31 (0.13)	−50.81 (3.13)	28.91 (2.41)	−21.90 (2.48)

Table 8
Toxicological properties of the active compounds of mahogany seed.

Compounds	Respiratory toxicity	Reproductive toxicity	Nephrotoxicity	Skin sensitization	Carcinogens
Glycidyl oleate	Non-toxic	Non-toxic	Non-toxic	Non-sensitive	Non-carcinogens
Glycidyl Palmitoleate	Non-toxic	Non-toxic	Non-toxic	Non-sensitive	Non-carcinogens
Acarbose (Control)	Non-toxic	Toxic	Non-toxic	Non-sensitive	Non-carcinogens

Table 9
ADME properties of the active compounds of mahogany seed.

Compounds	Molecular weight (g/mol)	Num. of H-bond acceptors	Num. of H-bond donor	log *p*	Molar refractivity	Veber's filter Num. of rotatable bonds	TPSAh (Å^2)	Lipinski's rule of five violations	Veber's rule of violations
Glycidyl oleate	338.52	3	0	5.89	102.84	18	38.83	0	1
Glycidyl Palmitoleate	310.47	3	0	5.14	93.23	16	38.83	0	1
Acarbose (Control)	307.34	8	7	−2.18	71.23	3	142.64	0	1

2)The paper is not currently being considered for publication elsewhere.
3)The paper reflects the authors' own research and analysis in a truthful and complete manner.
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CRediT authorship contribution statement

Mushawwir Taiyeb: Writing – review & editing, Writing – original draft, Validation, Formal analysis, Data curation, Conceptualization. **Hartati Hartati:** Writing – original draft, Investigation. **Arwansyah Arwansyah:** Writing – original draft, Validation, Methodology, Data curation. **Dahlia:** Resources, Project administration, Investigation. **Abd. Muis:** Validation, Supervision, Methodology, Funding acquisition. **A. Mu'nisa:** Software, Project administration, Investigation. **Abdur Rahman Arif:** Visualization, Validation, Software. **Liza Md Salleh:** Methodology, Investigation.

Declaration of competing interest

There are no conflicts of interest declared by the authors.

Acknowledgment

This work was supported by PNBP Percepatan Profesor UNM scheme with Grant number 1245/UN36.11/LP2M/2023.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.imu.2024.101517.

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