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In Silico Analysis of the Potential of *Mangifera Sumatrana* as an Antidiabetic

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Abstract: Diabetes is the most common endocrine disorder worldwide that causes heredity, radiation, other disorders, and pancreatic diseases. Various developed synthetic drugs and protein inhibitors treat diabetes, but they have side effects that are at risk of harming health. Alternative drugs from the plant are urgently necessary. Mangifera sumatrana is one of the potential candidates for antidiabetic therapy. This study used an in silico approach and aimed to determine bioactivity and pharmacokinetic properties of ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles, protein–protein interaction, and molecular dynamics. This assay used M. sumatrana compounds and target proteins related to diabetes, especially aldose reductase, alpha-glucosidase, and sodium-glucose co-transporter 2. The results showed that the compounds of M. sumatrana have bioactivity as anti-inflammatory, antioxidant, free radical scavenger, NO antagonist, and antidiabetic. The compounds conformed to several pharmacokinetic standards, and four were non-hepatotoxic. Compound (1S,2S,7R,16S,18S,20R)-11-Hydroxy-20-(hydroxymethyl)-16-methoxy-6,6,7,20-tetramethyl-10,18-bis(3-methyl-2-buten-1-yl)-3,8,19-trioxahexacyclo[14.4.1.02,14.02,18.04,12.05.9]henicosa-4,9,11,14-tetraene-13,17-dione and gardenin E have lower binding affinity against aldose reductase and alpha-glucosidase. 4,7,7-trimethyl-3-oxobicyclo(2.2.1)heptane-1-carboxylic acid and 2-heptyl-5-methylisophthalic acid are predicted to be stable against potency, and four compounds of M. sumatrana – to have the potential as the best candidates for aldose reductase, alpha-glucosidase, and SGLT-2 inhibitors against diabetes. Information from this study can be the basis for developing plant-based drugs without side effects for people with diabetes on an industrial scale.

Keywords: *Mangifera sumatrana*, diabetes mellitus, molecular docking, plant-based inhibitors, protein-targeted drugs.

蘇門答臘芒果抗糖尿病潛力的電腦分析

摘要：糖尿病是世界最常見的內分泌疾病，會導致遺傳、放射、其他疾病和胰臟疾病。各種已開發的合成藥物和蛋白質抑制劑可以治療糖尿病，但它們具有危害健康的副作用。迫切需要來自植物的替代藥物。蘇門答臘芒果是抗糖尿病治療的潛在候選人之一。本研究採用電腦模擬方法，旨在確定阿德梅特（吸收、分佈、代謝、排泄和毒性）特徵、蛋白質-蛋白質相互作用和分子動力學的生物活性和藥物動力學特性。本實驗使用蘇門答臘海藻化合物和與糖尿病相關的目標蛋白，特別是醛糖還原酶、α-葡萄糖苷酶和鈉-葡萄糖共轉運蛋白 2。結果表明，蘇門答臘海藻化合物具有抗發炎、抗氧化、自由基清除劑、不拮抗劑和抗糖尿病劑。

這些化合物符合多項藥物動力學標準，其中四種無肝毒性。化合物(1S,2S,7 右,16S,18S,20 右)-11-羥基-20-(羥甲基)-16-甲氧基-6,6,7,20-四甲基-10,18-雙(3-甲基-2)-丁烯-1-基)-3,8,19-三氧雜六環[14.4.1.02,14.02,18.04,12.05.9] 赫尼科薩-4,9,11,14-四烯-13,17-二酮和栀子 E 具有較低的對醛糖還原酶和α-葡萄糖苷酶的結合親和力。4,7,7-三甲基-3-氧雙環(2.2.1)庚烷-1-羧酸和 2-庚基-5-甲基間苯二甲酸預計對效力穩定，並且蘇門答臘芒果的四種化合物– 具有有望成為醛糖還原酶、α-葡萄糖苷酶和 SGLT-2 糖尿病抑制劑的最佳候選者。這項研究的資訊可以作為工業規模開發對糖尿病患者無副作用的植物性藥物的基礎。

关键词：蘇門答臘芒果，糖尿病，分子對接，植物抑制劑，蛋白質標靶藥物。

1. Introduction

Diabetes is the most common endocrine disorder worldwide. Approximately 537 million (10.5%) of the world population adults (20-79 years) in 2021 will be living with diabetes mellitus (DM). This number is projected to increase by 94% in 2045 in low- and middle-income countries. Indonesia is ranked the fifth most number of people with DM, about 19.5 million, after China, India, Pakistan, and the United States [1]. Diabetes is a heterogeneous metabolic disorder characterized by hyperglycemia due to impaired insulin secretion, defective insulin action, or both, and is associated with microvascular complications and a risk for cardiovascular disease (CVD) [2]. DM has two main types: Type 1 autoimmune or insulin-dependent (T1DM) and Type 2 or noninsulin-dependent (T2DM).

The primary causes of DM are heredity, radiation, disorder, and pancreatic diseases [3]. Numerous proteins contribute to the development of DM, including aldose reductase, glucokinase, fructose 1, 6-bisphosphatase, cytochrome 450, dipeptidyl-peptidases, 11β-hydroxysteroid dehydrogenase, glutamine fructose-6- phosphate amidotransferase, glutamine fructose-6-phosphate amidotransferase, protein tyrosine phosphatases, protein kinase B, alpha-glucosidase, insulin receptor substrate, AMP-activated protein kinase, glucose transporter, interleukin-1 receptor-associated kinase, and cholesterylester transfer Q3 protein [4]. Aldose reductase (AR) is the key enzyme of the polyol pathway that reduces glucose to sorbitol in the presence of NADPH and is significantly associated with diabetic retinopathy (DR) and hyperglycemia [5]. Alpha-glucosidase (AG) is an enzyme that hydrolyzes carbohydrates into glucose and causes the most T2DM, as indicated by high blood glucose levels (hyperglycemia) [6]. Sodium–glucose co-transporter 2 (SGLT-2) is a protein expressed in the proximal convoluted tubule of the kidneys, where it activates at a high capacity for the reabsorption of filtered glucose; hyperactivity of SGLT-2 causes excessive glucose uptake [7]. T1DM and T2DM have been treated with several modern medications, such as synthetic protein inhibitors and oral antidiabetic agents. Further research has reported that these drugs have some harmful effects, including urinary tract infections, genital infections, dementia, hypoglycemia, lipodystrophy, headaches, and nasopharyngitis [8, 9]. Therefore, there is an urgent need to create a safe, effective natural alternative with minimal side effects and relatively low costs [10].

Mangifera sumatrana (pauh) is an endemic Sumatran semi-wild mango with potential as a plant-based drug. The fruit of this species is less desirable because of its sour taste and strong aroma. Despite this, *M. sumatrana* has high antioxidant activity (gallic acid and quercetin) and potential as an anticancer agent [11, 12]. This species is only found in lowland areas (less than 100 m a.s.l.) in Sumatra and is still commonly found in Riau Province [13]. The availability of this plant in nature supports its potential as a primary ingredient for drugs without risking extinction. In contrast, wild relatives such as M. magnifica are only found in forests and have limited samples. *M. sumatrana* contains several compounds from the alkaloid, alkane, amino acid, benzene, benzoic acid, and fatty acid groups [14]. *M. sumatrana* and its metabolites have great potential as an antidiabetic drug and protein-targeted inhibitor.

One of the comprehensive methods to discover novel ligands with therapeutic applicability is by using computational tools such as in silico molecular docking. The in silico virtual screening method is an optimal way to investigate and assess a plant's potential as a drug, especially in this research against multiple diabetes targets, in a rapid manner. Molecular docking is a structure-based modeling technique that predicts the interaction between targeted proteins and ligands. They evaluated the binding site for a particular receptor and the affinity of the interaction based on a scoring entity. As part of the investigation of novel AR, AG, and SGLT-2 inhibitors from *M. sumatrana*, we also investigated their in silico bioactivity and pharmacokinetic properties using ADMET (absorption, distribution, metabolism, and excretion and toxicity) profiles, protein–protein interactions, and molecular dynamics. The results of this study can serve as a

foundation for developing wild mango species as a standardized herbal medicine, especially as an antidiabetic with fewer side effects.

2. Methods

The research had several steps to perform molecular docking. The flowchart illustrates the methods (Fig. 1).

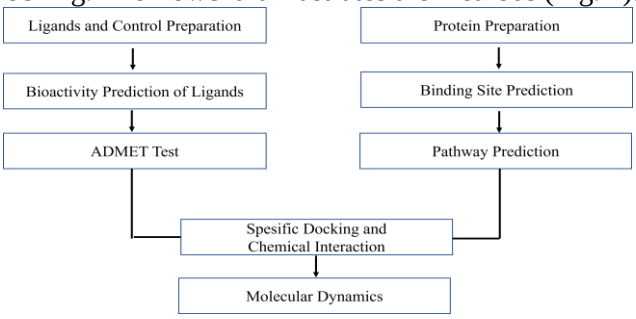

Fig. 1 Research flowchart

2.1. Ligands and Control Preparation

Test compounds were obtained from the profiling LCMS results of *Mangifera sumatrana* leaf extract. The 3D structures of the compounds were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) and ChemSpider (https://chemspider.com) databases. Compounds were prepared by optimizing their conformations using the Open Babel 2.3.1 plug-in integrated with PyRx 0.9 software for ligands obtained from PubChem [15]. In addition, ligand compounds in ChemSpider were downloaded in .mol file format and converted to the CADD Group Chemoinformatics Tools and User Services (CACTUS) website (https://cactus.nci.nih.gov/translate) to obtain Canonical SMILES. After refinement, the compounds were saved in the Protein Data Bank (.pdb) format. The control compound was obtained from the target protein's ligand and prepared in the same way as the active compound and from the original aldose reductase ligand, SGLT-2, and alpha-glucosidase. 3D and 2D visualizations were performed using Discovery Studio 2019 software. Ligands and proteins displayed in 3D structures provide an overview of the ligands and proteins before interacting. 3D visualization of protein–ligand interactions used the whole visualization and then focusing on the binding sites on the protein in 2D.

2.2. Protein Preparation and Binding Site Prediction

The 3D structures of the aldose reductase, SGLT-2, and alpha-glucosidase proteins were downloaded from the RCSB PDB database (https://www.rcsb.org/) and their respective IDs. The protein was prepared by removing contaminant molecules such as water and inherent ligands using Biovia Discovery Studio 2019 software [16]. Prediction of the binding sites on proteins was performed using the BIOVIA Discovery Studio software for control compounds or ligands, which included the interaction of protein amino acid residues with the original ligands or synthetic compounds. Each amino acid residue is recorded along with the target protein information.

2.3. Bioactivity Prediction of Ligands

Bioactivity prediction used the Pass Online web server (www.way2drug.com/passonline). Several categories of bioactivity included bioactivity related to anti-inflammatory, antioxidant, free radical scavenger, and NO antagonist; cancer-related bioactivity: anticarcinogenic, antimetastatic, antineoplastic, apoptotic agonist, and treatment of cancer-related diseases; diabetes-related bioactivity such as anti-DM, anti-DM 1, anti-DM 2, and antiobesity. The value used is Pa. compounds with a certain potential bioactivity if Pa>Pi and Pa>0.3 [17].

2.4. ADMET Test

The ADMET test determines a ligand compound's pharmacokinetic properties and toxicity as a drug candidate. ADMET aspects broadly include absorption, distribution, metabolism, excretion, and toxicity, which are essential in assessing drug safety and toxicity. ADMET analysis was performed by copying the Canonical SMILES of the ligand compound on the pkCSM website to obtain information regarding pharmacokinetic aspects and toxicity [18].

2.5. Pathway Prediction

The proteins interacting with the three target proteins were analyzed using Cytoscape 3.7.2 software and the STRING database (https://string-db.org/). Pathway prediction used the DAVID web server (Database for Annotation, Visualization, and Integrated Discovery) (https://david.ncifcrf.gov/) by inputting the proteins that appeared in the protein– protein interaction analysis.

2.6. Spesific Docking and Chemical Interaction

Molecular docking used AutoDock Vina, integrated with the PyRx 0.8 software. The selected docking result has the lowest binding affinity in each mode. The docking carried out is a specific docking that only predicts ligand interactions in the area of the active protein site. The binding affinity value indicates the stability of the interaction between the protein and the ligand. The lower the binding affinity value, the more stable the protein– ligand interaction [19].

Visualizing docking results used Biovia Discovery Studio 2019 software. The chemical interactions displayed are hydrogen bonds, hydrophobic, electrostatic, and unfavorable. Interactions that produce many hydrogen bonds are considered stable because hydrogen bonds are the strongest of the other types of bonds in molecular docking [20].

2.7. Molecular Dynamics

Molecular dynamic simulation used the CABS-flex 2.0 web server

(http://biocomp.chem.uw.edu.pl/CABSflex2) with parameters set according to the default web server. The results displayed are root mean square fluctuation) values which represent the stability of the protein after interacting with the ligand.

3. Results and Discussion

3.1. *Mangifera Sumatrana* Compounds

Table 1 presents f total of 15 compounds contained in the ethanol and dichloroethanol extracts of *Mangifera sumatrana*. Each compound identification used Pubchem and Chemspider databases. The 3D structures of the compounds are displayed in stick form and atomic coloring is used (Supplementary Fig. 1).

3.2. Structure and Binding Site of the Protein

The binding site is a specific area with the lowest energy on the protein, where the ligand and protein bind and undergo a chemical reaction. This active side can be found in clefts, grooves, or pockets composed of amino acid residues. These residues act as donors to ligands; thus, interactions occur [21]. The binding sites of Aldose reductase are Gly18, Thr19, Trp20, Lys21, Asp43, Val47, Tyr48, His110, Trp111, Ser159, Asn160, Gln183, Trp209, Ser201, Pro211, Leu212, Gly213, Ser214, Pro215, Asp216, Trp219, Ala245, Ile260, Pro261, Lys262, Ser263, Val264, Thr265, Arg268, Glu271, Asn272, Val297, Cys298, Ala299, Leu300, Leu301, Ser302. The binding sites of SGLT-2 are His80, Glu99, Ser287, and Gln457, whereas the binding sites of alpha-glucosidase are Asp404, Arg600, Asp616, His674.

The 3D structure of the protein is displayed in a ribbon style with secondary structure coloring Red represents the helix structure, light blue represents the beta-sheet structure, white represents the loop structure, and green represents the coil structure (Fig. 2). The information about coverage in molecular docking is Aldose reductase (Center X:16,2315; Y:-3,7300; Z:47,2612 and Dimension X:27,4132; Y:24,3293; Z:39,9807), SGLT-2 (Center X:123,673; Y:110,588; Z:105,592 and Dimension X:14,958; Y:17,431; Z:20,234) and Alpha-glucosidase (Center X:-18,321; Y:-30,199; Z:97,052 and Dimension X:32,305; Y:23,081; Z:26,209).

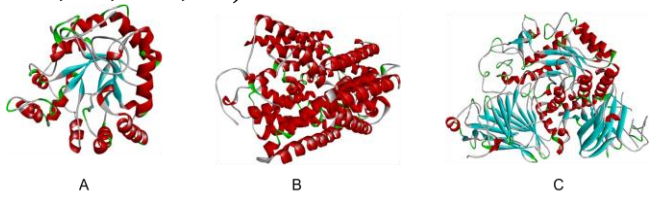

Fig. 2 3D structure of target protein: A. aldose reductase, B. SGLT-2, C. alpha glucosidase

3.3. Bioactivity Prediction

Compounds predicted for bioactivity using PASS to evaluate the overall bioactivity of all substances based on their chemical structure based on the structure–activity relationship (SAR) [22]. The predicted results of compound bioactivity are shown in Pa (potential activity) and Pi (potential inhibitory) values. Seven compounds of *M. sumatrana* have metabolic activity related to target proteins with a Pa value of more than 0.3 (Supplementary Table 2).

Gardenin E (CID 3084508) has intense potential activity as an anti-inflammatory, free radical scavenger, and anti-diabetic agent. Its bioactivity as an anti-inflammatory and free radical scavenger has a Pa>0.7, which means that the compound has very high biological activity. Gardenin E has good radical scavenging activity [23].

Khelloside (CID 441966) is predicted to have the most effective antioxidant, NO antagonist, and anti-diabetes mellitus activities. The khelloside compound belongs to the furochromone group. Other compounds, such as CID 558757, CID 11261702, CID 39516134, and CID 509193, had at least one potential bioactivity related to the target protein.

Table 1 Compounds, CIDs, and database sources of *M. sumatrana*

Compound formulas	Compound names	CID	Sources
Metanol Extract			
C13H22N5O7	(2R,3R)-2,3-Dihydroxysuccinic acid - (2E)-6-amino- 2-imino-4-(1-piperidinyl)-1(2H)-pyrimidinol (1:1)	59149412	PubChem
C20H16N4O7	5-[(4-Meth yl-2-nitrophenoxy)methyl]-N'-[(Z)-(4-nitrophenyl)methylene] - 2-furohydrazide	4782402	ChemSpider
C19H18O9	Gardenin E	3084508	PubChem
C19H20O10	Khelloside	441966	PubChem
C19H19N9O	(5-Methyl-1-phenyl-1H-pyrazol-4-yl){3-[4-(2H-1,2,3- triazol-2-ylmethyl)-1H-1,2,3-triazol-1-yl]-1-azetidinyl}methanone	39516134	ChemSpider
C11H16O3	4,7,7-Trimethyl-3-Oxobicyclo(2.2.1)Heptane-1- Carboxylic Acid	558757	PubChem
C22H33N5O6	Phenylalanylglutaminylglycylisoleucine	20004055	PubChem
C21H39NO8	methyl 9-[(2S,3S,4S,5R)-5-[[(2R,3R,4R)-2-ethyl-3,4-dihydroxy-pyrrolidin-1-yl]methyl]-3,4-dihydroxy- tetrahydrofuran-2-yl]oxynonanoate	509193	PubChem
C26H29N5O8	N2-[(2S)-2-(2,4-Dioxo-1,4-dihydro-3(2H)-quinazolinyl)-3-phenylpropanoyl]-L-glutaminyl-L- threonine	95372822	PubChem
Dicloromethanol Extract			
C16H22O4	2-Heptyl-5-methylisophthalic acid	1473490	ChemSpider
C34H43O8	(1S,2S,7R,16S,18S,20R)-11-Hydroxy-20-(hydroxymethyl)-16-methoxy-6,6,7,20-tetramethyl- 10,18-bis(3-methyl-2-	11261702	PubChem

	buten-1-yl)-3,8,19-trioxahexacyclo [14.4.1.02,14.02,18.04,12.05,9]henicosa-4,9,11,14-te traene-13,17-dione		
C28H27N	N-Phenyl-N,4-bis(1-phenylethyl)aniline	44151100	PubChem
C35H36N4O5	N-{2-[(11aS)-5-(4-Isopropylphenyl)-1,3-dioxo- 5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido[3,4-b]indol-2(3H)-yl]benzoyl}-L-isoleucine	17470794	ChemSpider
C36H35N	N,4-Bis(1-phenylethyl)-N-[4-(1- phenylethyl)phenyl]aniline	44149948	PubChem
C36H38N4O5	1-(Cyclohexylmethyl)-5'-O-tritylinosine	17241457	ChemSpider

3.4. ADMET Test of *M. Sumatrana* Compounds

Pharmacokinetics and toxicity prediction is essential in understanding the disposition of drug molecules in an organism because it predicts the effects caused. For example, when the absorption of a drug is not good, it will affect the distribution and metabolism process. Drug absorption depends on several factors or parameters such as water solubility, membrane permeability (indicated by colon cancer cell line (Caco-2)], human intestinal absorption (HIA), skin permeability levels, and P-glycoprotein substrate or inhibitor. The water solubility parameter reflects the solubility of molecules in water at 25°C. CID 558757 has the highest water solubility of -2.006 (Supplementary Table 3). All the relative compounds had high HIA values (>30%) and high skin permeability. The high HIA value illustrates that the compound is well absorbed in the human intestine. Based on Caco-2 parameters, three compounds meet these parameters. The compound CID 558757 is predicted to have high Caco-2 permeability, so it has the gastrointestinal permeability of a drug. P-glycoprotein (P-gp) is an ATP-binding cassette (ABC) transporter on the cell membrane that acts as a barrier in cells by eliminating toxins. The compounds CID 558757 and CID 1473490 do not have characteristics of substrates or P-gp inhibitors; thus, they are predicted to have therapeutic abilities (Yeni and Rachmania 2022). These two compounds also fulfill all absorption parameters, meaning they will be easily distributed to the target location.

Compound CID 11261702 meets all the indicators of the distribution parameters (Supplementary Table 3). Volume distribution (VDss) is a theoretical volume required by a drug to predict the value of the total dose of the drug, which would need to be uniformly in blood plasma. The higher the VDss, the more a drug is distributed in tissue rather than plasma. The test compounds' VDss ranged from -0.706 to 0.47 (log L/kg). In addition, the unbound fraction (D2) indicates the capacity of the drug to bind to proteins in the blood so that the drug has different efficacy in diffusion through the cell membrane [24]. Another parameter in distribution prediction is the blood barrierpermeability. The BBB parameter is important for determining the ability of a drug to cross into the brain barrier because it helps minimize side effects or toxicity. Seven compounds were tested, five of which had a small value, and two others had BBB values above -1.1, indicating that they could penetrate the BBB moderately. One of them is compound CID 11261702, which had a BBB value of 0.731 (Log BB value > 0.3). Increased blood–brain barrier permeability (BBB) plays a role in surface exchange between blood and the central nervous system. BBB values can also be used to estimate the capacity of drugs to reach the central nervous system [24].

This assay also measures metabolic parameters based on the inhibition ability targeting the phase 1 CYP450 family (CYP2D6, CYP3A4, CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) that are involved in 90% of metabolic enzymatic reactions. As many as four compounds meet the metabolic parameters because they are not inhibitors of CYP450 enzymes. They do not seriously impact the body during consumption, and it can be predicted that the test compounds will be metabolized by cytochrome P450 enzymes [25]. The compounds presented in Table 5 are CID 441966, CID 558757, CID 509193, and CID 1473490. Some other compounds, such as CID 3084508, CID 39516134, and CID 11261702, inhibited CYP450 activity, leading to low clearance and accumulation of metabolites in the body.

Table 4 presents the computed excretion properties of the compounds. Excretion involves the parameters clearance (E) and renal OCT2 substrate. Clearance (E) indicates the ratio of drug elimination rate to plasma drug concentration in units of log mL/min/kg. The total clearance value of the test compounds ranges from -0.187 to 1.306. Compound CID 1473490 has the highest total clearance value. The total clearance value indicates that the drug can be excreted from the central compartment of the body without any significant mechanism [26]. In contrast, renal uptake of organic cation transporter 2 (OCT2) is essential for drug disposition and renal clearance. If a drug inhibits OCT2, it will have a negative effect. The prediction results show that all test compounds do not inhibit OCT2 that predicted not to have side effects or contraindications.

The toxicity test results show that all compounds are predicted not to show mutagenic effects according to the Ames test (Supplementary Table 2). Compounds without mutagenesis effects are not predicted to be carcinogenic [27]. Compound 4 CID 558757 has the highest maximum daily dose of 0.956 mg/kg/day. CID 11261702 had the highest LD50 of 3,302 mol/kg. Some compounds, such as CID 441966, CID 39516134, and CID 509193, were toxic to the liver, causing disrupted normal function of the liver.

Based on the results of the five ADMET parameters, it was found that each M. sumatrana compound fulfills only some ADMET parameters. Therefore, compounds

that are non-toxic to the body will be filtered for further analysis using the molecular docking method. Four compounds are non-toxic to the body, namely CID 3084508 (flavonoids group), CID 558757 (alkaloids member), CID 1473490 (benzoic acid member), and CID 11261702 (fatty acid member). Virtual screening analysis of these four compounds is needed to determine compounds that have compatibility and efficacy against target proteins through molecular docking.

3.5. Protein-Protein Interaction (PPI) and Pathway Prediction

The results of the target protein interaction analysis showed that aldose reductase (AR), SGLT2 (SLC5A4), and-glucosidase (GABPA) proteins interact with 30 other proteins. These proteins are associated with cell proliferation, such as cyclin D1, PIK3R1, SRC, and MYC (Fig. 3A). The proteins that interact with these target proteins play a role in the signaling pathway of thyroid hormone, prostate cancer, cancer signaling pathway, etc. (Fig. 3B). The proteins that interacted most with aldose reductase (AR), SGLT2 (SLC5A4), and-glucosidase (GABPA) with proteins involved in the cancer signaling pathway were 13 proteins, and thyroid hormone signaling was 12 proteins. The interaction between the target proteins that cause diabetes and various other proteins is predicted to be a cause of complications in patients with diabetes. Diabetes causes several cancers, such as pancreatic, liver, colon, breast, and endometrial cancers [28].

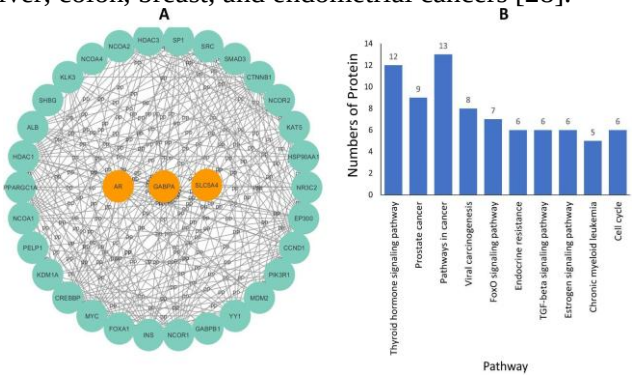

Fig. 3 Protein–protein interaction and pathway prediction: A. Protein–protein interaction. Orange color shows the target protein, and light blue color shows the proteins that interact with the target protein; B. Ten pathways affected by target proteins and proteins that interact with target proteins

3.6. Molecular Docking, Chemical Interactions, and Visualization

Four compounds are non-toxic to the body based on the ADMET test needed to determine the compatibility and efficacy against target proteins through molecular docking. Docking results are closely related to the binding affinity value (affinity energy 'ΔG') that indicates how strong the bond is between the protein and the ligand. The smaller or lower the binding affinity value (the more negative), the easier the ligand binds to the protein and the more potential it has to affect the protein because it requires little energy when binding.

The aldose reductase (AR) inhibitor has a binding affinity value of -7.8. Based on the molecular docking results, CID 11261702 had the lowest binding affinity value and was smaller than the inhibitor at -9.1 (Table 2), indicating that these compounds have stronger binding affinities toward Aldose reductase. This compound also showed a lower value than other test compounds and inhibitors against alpha-glucosidase, followed by CID 3084508. These two compounds demonstrate the most stable bonds to aldose reductase and alpha-glucosidase.

In contrast, the other compounds had a higher binding affinity value than the inhibitor. The compound CID 558757 projected a lower binding affinity value than the SGLT-2 inhibitors simulated through molecular docking (Table 2). In addition, CID 1473490 showed the same binding affinity value as the SGLT-2 inhibitor, indicating that the compound has the same binding ability as the inhibitor to the target protein.

Docking results between aldose reductase and test compounds show that chemical interactions occur on the active or functional side (Fig. 2). The chemical interaction between the test compounds CID 11261702 and CID 3084508 with aldose reductase occurs at several active side positions and has more varied chemical interactions than the inhibitor. It is directly proportional to the binding affinity value that is more negative so that the ligand– protein complex formed is more stable. In addition, hydrogen bonds play an essential role in the stability and turnover of cellular protein activity. CID 3084508 compounds have four hydrogen bonds to aldose reductase (Supplementary Table 4), which are more varied than the bonds of native ligands.

The same bond position as the inhibitor indicates that the test compound has activity similar to that of the inhibitor, inhibiting the target protein's activity. The visualization results show that some residues of the compound CID 11261702 and the interacting CID 3084508 have similarities with the native ligand. The compound is predicted to have good antidiabetic activity against the target protein aldose reductase.

The interaction between SGLT-2 and the test compound shows that the chemical interaction is more stable than the inhibitor (Fig. 2). CID 558757 shows a more negative binding affinity value so that the ligand–protein complex formed is more stable, which is also supported by the presence of more hydrophobic interactions than those of the inhibitor [29]. The residues that form hydrophobic bonds are Ala102, Ala102, Leu283, Leu283, Tyr290, Trp291, and Phe453. These residues are nonpolar amino acids that tend to form hydrophobic interactions. CID 1473490 showed the same binding affinity value as the inhibitor but formed an electrostatic interaction at residue Ala284. Electrostatic interaction plays a role in the

stability of the ligand to the receptor and contributes to the formation of protein conformation [30].

Alpha-glucosidase shows that chemical interactions occur on the active side toward the inhibitor and CID 3084508 (Fig. 4). However, CID 3084508 only interacts with the active site of Asp616 via electrostatic bonds. The role of electrostatic bonds is important in the conformational changes, structure, and stability of proteins. In addition, CID 11261702 has the most negative binding affinity even though the chemical bonds positioned are less varied and do not interact with the binding site. The distance between amino acid residues and ligands is another factor that determines molecular docking results [31].

Table 2 Binding affinity molecular docking of the protein–ligand

Compounds	Aldose reductase	SGLT-2	Alfa glucosidase
Inhibitor	-7,8	-6,3	-5,8
CID 3084508	-7,6*	-1,7	-6,4*
CID 558757	-5,9	-7.4*	-5,4
CID 1473490	-6,9	-6,3*	-6,1
CID 11261702	-9,1*	27,0	-7.2*

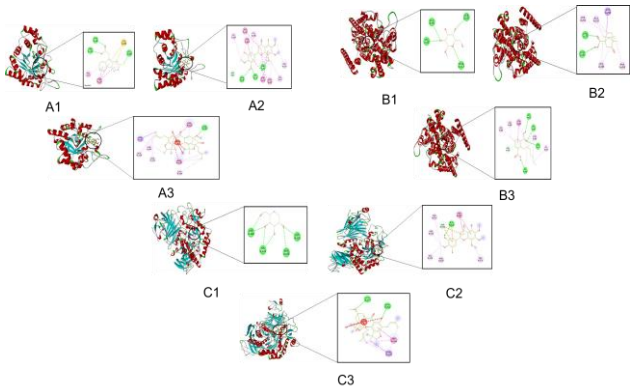

Fig. 4 A. Interaction between aldose reductase and A1 inhibitor, A2 CID 3084508 , and A3 CID 11261702; B. Interaction between SGLT-2 and B1 inhibitor, B2 CID 558757 and B3 CID 1473490; C. Interaction between alpha-glucosidase and C1 inhibitor, C2 CID 3084508 and C3 CID 11261702

3.7. Molecular Dynamics

The molecular dynamic results are displayed as Root Mean Square Fluctuation (RMSF) values. This value shows the fluctuation of the amino acid residues that make up the receptor during the simulation process; thus, it can represent the flexibility of the residues [32]. Residues with high fluctuation and flexibility are unstable because they change their position the most during the dynamics simulation. These residues donot play a role in the binding site. Meanwhile, residues that do not provide high flexibility are stable and play an essential role in the active binding site with the ligand. Based on the molecular dynamics results, all complexes achieved an RMSF range between 1 and 3 Å. The Aldose reductase–ligand complex shows that most residues have an RMSF value of less than 3 Å, indicating that the protein is stable when interacting with the ligand (Fig. 5A). Similarly, in the alpha glucosidase–ligand and SGLT2–ligand complexes, most residues had RMSF values below 3 Å (Fig. 5B and C).

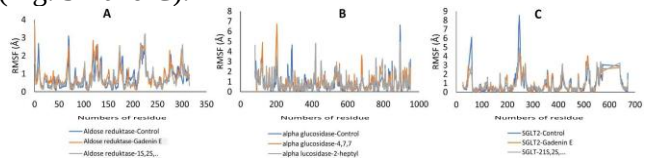

Fig. 5 Results of dynamic molecular analysis in the form of RMSF: A. Aldose reductase–ligand complex, B. Alpha glucosidase–ligand, C. SGLT2–ligand

4. Conclusion

This study proved that *Mangifera sumatrana* has potential as an antidiabetic based on a molecular docking study. The compounds of *M. sumatrana* have bioactivity as anti-inflammatory, antioxidant, free radical scavenger, NO antagonist, and anti-diabetic. Four compounds were non-hepatotoxic and had a lower binding affinity that showed stable potency as antidiabetic. (1S,2S,7R,16S,18S,20R)-11-Hydroxy-20-(hydroxymethyl)-16-methoxy-6,6,7,20-tetramethyl-10,18-bis(3-methyl-2-buten-1-yl)-3,8,19-trioxahexacyclo[14.4.1.02,14.02,18.04,12.05.9]henicosa-4,9,11,14-tetraene-13,17-dione and gardenin E potential as aldose reductase and alpha glucosidase inhibitors, while 4,7,7-Trimethyl-3-Oxobicyclo(2.2.1)Heptane-1-Carboxylic Acid and 2-Heptyl-5-methylisophthalic acid potential as SGLT-2 inhibitors. This result is a new finding that other studies have not reported. In this regard, our study can pave the way for a new candidate based on plants in developing potent inhibitors for future therapeutic intervention against diabetes without side effects. This study investigated the potential of *M. sumatrana* on several target proteins that are directly related to diabetes type 1 and type 2. However, it is limited and does not include several other target proteins. Further research on other target proteins and in vitro and in vivo studies are needed to strengthen the results of this study.

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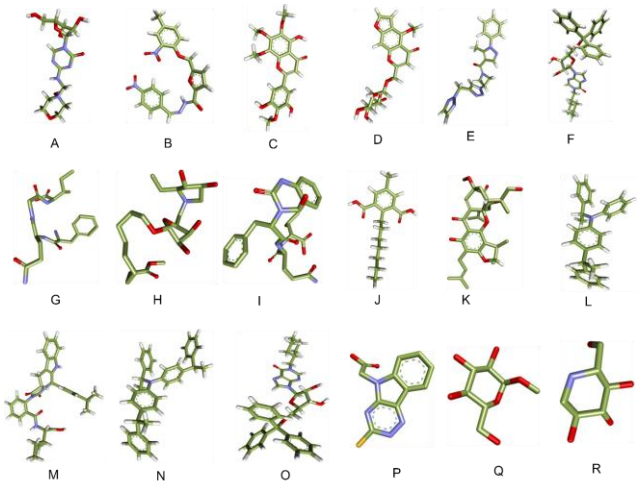

Supplementary Fig. 1 3D visualization of the compound structure (C atoms are colored green, O atoms are colored red, and H atoms are colored white): A. (2R,3R)-2,3-dihydroxysuccinic acid-(2E)-6-amino-2-imino-4-(1-piperidinyl)-1(2H)-pyrimidinol (1:1); B. 5-[(4-methyl-2-nitrophenoxy)methyl]-N'-[(Z)-(4-nitrophenyl)methylene]-2-furohydrazide; C. Gardenin E; D. Khelloside; E. (5-methyl-1-phenyl-1H-pyrazol-4-yl){3-[4-(2H-1,2,3-triazol-2-ylmethyl)-1H-1,2,3-triazol-1-yl]-1-azetidinyl}methanone; F. 4,7,7-trimethyl-3-oxobicyclo(2.2.1)heptane-1-carboxylic acid; G. Phenylalanylglutaminylglycylisoleucine; H. Methyl 9-[(2S,3S,4S,5R)-5-[[(2R,3R,4R)-2-ethyl-3,4-dihydroxy-pyrrolidin-1-yl]methyl]-3,4-dihydroxy-tetrahydrofuran-2-yl]oxynonanoate; I. N2-[(2S)-2-(2,4-dioxo-1,4-dihydro-3(2H)-quinazolinyl)-3-phenylpropanoyl]-L-glutaminyl-L-threonine; J. 2-heptyl-5-methylisophthalic acid; K. (1S,2S,7R,16S,18S,20R)-11-hydroxy-20-(hydroxymethyl)-16-methoxy-6,6,7,20-tetramethyl-10,18-bis(3-methyl-2-buten-1-yl)-3,8,19 trioxahexacyclo [14.4.1.02,14.02,18.04,12.05,9] henicosa-4,9,11,14-tetraene-13,17-dione; L. N-phenyl-N,4-bis(1-phenylethyl)aniline; M. N-{2-[(11aS)-5-(4-isopropylphenyl)-1,3-dioxo-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido[3,4-b]indol-2(3H)-yl]benzoyl}-L-isoleucine; N. N,4-bis(1- phenylethyl)-N-[4-(1-phenylethyl)phenyl]aniline; O. 1-(cyclohexylmethyl)-5'-O-tritylinosine; P. (3-thioxo-2,3-dihydro-5H-[1,2,4]triazino[5,6-b]indol-5-yl)acetic acid; Q. Methyl alpha-D-glucopyranoside; R. 1-deoxynojirimycin

Supplementary Table 2 Potential bioactivity of *Mangifera sumatrana* compounds

Compounds	**Anti-inflammatory**	**Anti-oxidant**	**Free radical scavenger**	**NO Antagonist**	**Anti-DM**	**Anti-DM1**	**Anti-DM2**	**Anti-DM Symptomatic**	**Anti-Obesity**
(2R,3R)-2,3-dihydroxysuccinic acid - (2E)-6-amino-2-imino-4-(1-piperidinyl)-1(2H)-pyrimidinol (1:1) (CID 59149412)	The compound cannot be identified by the database								
5-[(4-methyl-2-nitrophenoxy)methyl]-N'-[(Z)-(4-nitrophenyl)methylene]-2-furohydrazide (CID 4782402)	-	-	-	-	-	-	-	-	-
Gardenin E (CID 3084508)	0,738	-	0,803	0,254	-	-	-	0,335	-
Khelloside (CID 441966)	0,608	0,717	0,682	0,465	0,555	-	-	0,217	-
(5-methyl-1-phenyl-1H-pyrazol-4-yl){3-[4-(2H-1,2,3-triazol-2-ylmethyl)-1H-1,2,3-triazol-1-yl]-1-azetidinyl}methanone (CID	0,322	-	-	-	0,158	-	-	-	0,522

39516134)									
4,7,7-trimethyl-3-oxobicyclo(2.2.1)heptane-1-carboxylic acid (CID 558757)	0,347	-	0,233	-	-	-	-	-	-
Phenylalanylglutaminylglycylisoleucine (CID 20004055)	0,239	-	-	-	-	0,192	-	-	-
Methyl 9-[(2S,3S,4S,5R)-5-[[(2R,3R,4R)-2-ethyl-3,4-dihydroxy-pyrrolidin-1-yl]methyl]-3,4-dihydroxy-tetrahydrofuran-2-yl]oxynonanoate (CID 509193)		0,267	0,201	0,126	0,440	-	-	-	-
N2-[(2S)-2-(2,4-Dioxo-1,4-dihydro-3(2H)-quinazolinyl)-3-phenylpropanoyl]-L-glutaminyl-L-threonine (CID 95372822)	-	-	-	-	-	-	-	-	-
2-heptyl-5-methylisophthalic acid (CID 1473490)	0,421	0,176	-	-	0,275	0,188	0,147	0,303	-
(1S,2S,7R,16S,18S,20R)-11-Hydroxy-20-(hydroxymethyl)-16-methoxy-6,6,7,20-tetramethyl-10,18-bis(3-methyl-2-buten- 1-yl)-3,8,19-trioxahexacyclo[14.4.1.02,14.02,18.04,12 .05,9]henicosa-4,9,11,14-te traene-13,17-dione (CID 11261702)	-	0,378	0,197	0,234	-	-	-	-	-
N-phenyl-N,4-bis(1-phenylethyl)aniline (CID 44151100)	-	-	-	-	-	-	-	-	-
N-{2-[(11aS)-5-(4-Isopropylphenyl)-1,3-dioxo-5,6,11,11a-tetrahydro-1H-imidazo[1',5':1,6]pyrido[3,4-b]indol-2(3H)-yl]benzoyl}-L-isoleucine (CID 17470794)	-	-	-	-	-	-	-	0,284	-
N,4-bis(1-phenylethyl)-N-[4-(1-phenylethyl)phenyl]aniline (CID 44149948)	-	-	-	-	-	-	-	-	-
1-(cyclohexylmethyl)-5'-O-tritylinosine (CID 17241457)	0,298	-	-	-	-	-	-	-	-

Note: Compounds marked in bold have bioactivity (Pa > 0.3).

Supplementary Table 3 ADMET test results M. sumatrana compound

Pharmacokinetics	**Parameters**	**A**	**B**	**C**	**D**	**E**	**F**	**G**
Absorption	Water Solubility	- 3,328	- 2,612	- 2,61	- 2,006	- 2,736	- 2,856	- 4,575
	Caco-2 Permeability	0,345	0,533	0,17	1,234	-0,202	0,972	1,102
	HIA	100	58,27	85,60	96,01	36,779	99,979	98,997
	Skin Permeability	- 2,736	- 2,75	- 2,743	- 2,732	- 2,944	- 2,735	- 2,743
	P-glikoprotein Substrat	Ye s	Ye s	No	No.	Ye s	No	Ye s
	P-glikoprotein I Inhibitor	No	No	Ye s	No.	No	No	Ye s
	P-glikoprotein II Inhibitor	Ye s	No	No	No.	No	No	Ye s
Distribution	VDss (Human)	0,47	-0,326	-0,272	-0,706	-0,36	-1,659	0,328
	fraction unbound (Human)	0,036	0,263	0,143	0,576	0,671	0,242	0,027
	BBB Permeability	-1,472	-1,44	-1,255	0,258	-1,215	-0,253	-0,731
	CNS Permeability	-3,496	-3,633	-3,662	-2,877	-3,95	-2,475	-2,386
Metabolism	CYP2D6 Substrates	No	No	No	No.	No	No	No
	CYP3A4 Substrat	No	No	Yes	No.	No	No	Yes
	CYP1A2 Inhibitors	Yes	No	Yes	No.	No	No	No
	CYP2C19 Inhibitors	No	No	No	No.	No	No	No
	CYP2C9 Inhibitors	No	No	No	No.	No	No	No
	CYP2D6 Inhibitors	No	No	No	No.	No	No	No
	CYP3A4 Inhibitors	No	No	No	No.	No	No	Yes
Excretion	Clearance Total	0,587	0,67	0,487	0,133	1,243	1,306	-0,187
	Organic Cation Transporter (OCT) 2 substrate	No	No	No	No.	No	No	No
Toxicity	Mutagenicity (Ames test)	No	No	No	No.	No	No	No
	Maximum Tolerated Dose (Human)	0,214	0,404	0,058	0,956	0,491	0,564	-0,557
	Rat Oral Acute Toxicity (LD50)	2,212	2,487	2,273	1,804	1,715	2,282	3,302
	Hepatotoxicity	No	Yes	Yes	No.	Yes	No	No

Notes: A - CID 3084508 'Gardenin E'; B - CID 441966 'Khelloside'; C - CID 39516134 '(5-methyl-1-phenyl-1H-pyrazol-4-yl){3-[4-(2H-1,2,3-triazol-2-ylmethyl)-1H-1,2,3 triazol-1-yl]-1-azetidinyl}methanone'; D - CID 558757 '4,7,7-trimethyl-3-oxobicyclo(2.2.1)heptane-1-carboxylic acid; E - CID 509193 'Methyl 9-[(2S,3S,4S,5R)-5-[[(2R,3R,4R)-2-ethyl-3,4-dihydroxy-pyrrolidin-1-yl]methyl]-3,4-dihydroxy-tetrahydrofuran-2-yl]oxynonanoate'; F - CID 1473490 '2-heptyl-5-methylisophthalic acid'; G - CID 11261702 '(1S,2S,7R,16S,18S,20R)-11-Hydroxy-20- (hydroxymethyl)-16-methoxy-6,6,7,20-tetramethyl-10,18-bis(3-methyl-2-buten-1-yl)-3,8,19-trioxahexacyclo[14.4.1.02,14.02,18.04,12.05 ,9]henicosa-4,9,11,14-te traene-13,17-dione'

Supplementary Table 4 Details of protein-ligand interactions with the best results

Proteins	**Compounds**	**Interaction position**		
		Hydrogen bonds	**Hydrophobic interactions**	**Electrostatic interaction**
Aldose reductase	Inhibitor (3-thioxo-2,3-dihydro- 5H-[1,2,4]triazino[5,6-b]indol-5- yl)acetic acid).	A:Tyr48, A:Trp111, A:Leu300	A:Trp20, A:Trp20, A:Trp20, A:Trp20, A:Val47	A:Cys298, A:Cys298
	Gardenin E	A:Trp20, A:Asp43, A:His110, A:Gln183	A:Trp20, A:Trp20, A:Trp20, A:Trp20, A:Trp20, A:Val47, A:Tyr48, A:Tyr48, A:Trp111, A:Phe122, A:Tyr209, A:Tyr209, A:Trp219, A:Ile260, A:Cys298, A:Cys298,	-
	(1S,2S,7R,16S,18S,20R)-11-Hydroxy-20-(hydroxymethyl)- 16-methoxy-6,6,7,20-tetramethyl-10,18-bis(3-methyl- 2-buten-1-yl)-3,8,19 trioxahexacyclo[14.4.1.02,14.02,18.04,12.05,9]henicosa 4,9,11,14-te traene-13,17-dione	A:Ser302, A:Ser302	A:Trp20, A:Trp20, A:Trp20, A:Tyr48, A:His110, A:His110, A:Trp111, A:Trp111, A:Phe122, A:Phe122, A:Phe122, A:Leu124, A:Trp219, A:Trp219, A:Trp219	-
SGLT-2	Inhibitor (methyl alpha-D-glucopyranoside)	A:His80, A:Glu99, A:Ser287, A:Gln457	-	-
	4,7,7-Trimethyl-3-Oxobicyclo(2.2.1)Heptane-1- Carboxylic Acid	A:Asn75, A:Glu99	A:Ala102, A:Ala102, A:Leu283, A:Leu283, A:Tyr290, A:Trp291, A:Phe453	-
	2-Heptyl-5-methylisophthalic acid	A:Asp616	A:Trp376, A:Trp481, A:Trp516, A:Phe649, A:His674	A:Ala284
	Inhibitor (1-deoxynojirimycin)	A:Asp404, A:Asp404, A:Arg600, A:Arg600, A:Asp616, A:His674, A:His674,	-	-
	Gardenin E		A:Trp376, A:Trp481, A:Trp481, A:Trp516, A:Trp613,	A:Asp518, A:Asp616, A:Asp616
Alpha-glukosidase		A:Asp518, A:Asp518	A:Trp613, A:Phe649, A:His674	
	(1S,2S,7R,16S,18S,20R)-11-Hydroxy-20-(hydroxymethyl)- 16-methoxy-6,6,7,20-tetramethyl-10,18-bis(3-methyl- 2-buten-1-yl)-3,8,19- trioxahexacyclo[14.4.1.02,14.02,18.04,12.05,9]henicosa- 4,9,11,14-te traene-13,17-dione	A:Arg411, A:Leu677	A:Trp481, A:Trp481, A:Phe525, A:Phe525, A:Phe525	-

Note: The underscore (_) indicates the same interaction position as the binding site.