Molecular Docking Study of Bioactive Compounds in Senggugu (*Clerodendrum serratum* (L.) Moon) as Antidiabetics

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Abstract

Senggugu has the potential to be a source of natural medicine through its compounds. Using in silico approaches is an effective strategy for exploring compounds from natural products in the screening process. In vivo studies on senggugu have indicated that the plant has antidiabetic activity, although the active compounds involved in this activity are unknown. This study aims to explore the content of bioactive compounds of Senggugu (*Clerodendrum serratum* (L.) Moon) and its mechanism of action as an antidiabetic in silico with Molegro Virtual Docker software, ChemDraw, visualization with Discovery Studio, and ADMET prediction with pkCSM. The study was conducted by simulating the molecular docking of 31 bioactive compounds in Senggugu (*Clerodendrum serratum* (L.) Moon) with comparison compounds using glibenclamide, miglitol, rosiglitazone, linagliptin, and empagliflozin. The validated target proteins comprised 5 (five) receptors with PDB ID codes 4YVP, 5NN6, 7AWC, 6Y0F, and 7VSI. Based on this study, the compound predicted to be active as an antidiabetic is [(1S,2S,6R,7S,11R)-11-hydroxy-5,9,13-trimethylidene-4-oxo-3,14-dioxatricyclo [9.2.1.02,6] tetradecan-7-yl]2-methylprop-2-enoate at receptor 4YVP with a rerank score of -107.663 kcal/mol with glibenclamide -94.8299 kcal/mol and [3-hydroxy-4-[(2R)-6-methylhept-5-en-2yl]phenyl]methyl3-methylbut-2-enoate at 5NN6 receptor with a rerank score of -87.8719 with miglitol -64.7212 kcal/mol.

Keywords: *antidiabetic, Clerodendrum serratum, in silico, Molegro virtual docker*

How to cite

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Highlights

1. This study investigates the potential of Senggugu (Clerodendrum serratum (L.) Moon) as a source of natural antidiabetic medicine.
2. An in silico approach, using computer simulations for molecular docking with Molegro Virtual Docker and predicting drug properties with pkCSM, was used to study the active compounds.
3. The study simulated the molecular docking of 31 Senggugu compounds against five validated antidiabetic protein receptors (PDB IDs: 4YVP, 5NN6, 7AWC, 6Y0F, and 7VSI), with glibenclamide, miglitol, rosiglitazone, linagliptin, and empagliflozin as comparison compounds.

4. [(1S,2S,6R,7S,11R)-11-hydroxy-5,9,13-trimethylidene-4-oxo-3,14-dioxatricyclo[9.2.1.02,6]tetradecan-7-yl]2-methylprop-2-enoate was identified as a promising antidiabetic compound, exhibiting a rerank score of -107.663 kcal/mol at receptor 4YVP, outperforming glibenclamide (-94.8299 kcal/mol).
5. Another possible antidiabetic compound, [3-hydroxy-4-[(2R)-6-methylhept-5-en-2yl]phenyl]methyl3-methylbut-2-enoate, had a rerank score of -87.8719 kcal/mol at the 5NN6 receptor, showing it works better than miglitol (-64.7212 kcal/mol).

Introduction

Diabetes mellitus is a medical condition that arises when the body is unable to process glucose effectively. This dysfunction may result from insufficient insulin production or impaired insulin function. The global prevalence of diabetes is increasing, making it a leading cause of various serious health complications, including cardiovascular diseases, kidney disorders, and ocular conditions. In Indonesia, diabetes ranks among the most prevalent non-communicable diseases (NCDs), with a consistent upward trend in prevalence observed each year. According to the Basic Health Research (Riskesdas), early detection of diabetes mellitus involves blood glucose testing among 95,900,441 individuals aged 40 years and older. As of June 2023, the coverage of early detection had reached 13,470,556 individuals (14.05%). The province of West Nusa Tenggara (NTB) recorded the highest early detection coverage at 55.86%, followed by Gorontalo at 48.42% and East Kalimantan at 22.37%. In contrast, the provinces with the lowest coverage were the Special Region of Yogyakarta (DIY) at 3.59%, Bali at 3.37%, and Papua at 1.43%. Unhealthy lifestyle choices such as imbalanced diets, insufficient physical activity, and increasing obesity rates have been identified as major risk factors contributing to the rising prevalence of diabetes in the population (Kemenkes, 2023).

Indonesia is the fourth highest country in the prevalence of diabetes mellitus, following the United States, China, and India. The population of individuals with diabetes in Indonesia is anticipated to rise substantially, by two to threefold, by 2030 relative to the year 2000. According to the latest data from the Data and Information Center of the Indonesian Ministry of Health, the International Diabetes Federation (IDF) estimates that by 2035, approximately 592 million people worldwide will be living with diabetes mellitus (Leonita & Muliani, 2015).

Clerodendrum serratum has significant potential for medicinal applications. The leaves of this plant contain various active compounds that may help reduce blood glucose levels. Research findings indicate that *C. serratum* holds promising prospects for development as a herbal medicine, particularly for addressing diabetes related conditions (Kar et al., 2014). A study conducted by Wang et al., 2018 demonstrated that the aqueous extract of *C. serratum* roots exhibits a significant anti-inflammatory effect and has potential for use in the treatment of allergies and inflammatory diseases such as asthma.

In *silico* research, computers are utilized to perform virtual simulations or experiments. Researchers employ specialized software to investigate biological, chemical, or pharmaceutical processes in greater detail. Commonly used *in silico* methods include molecular docking, molecular dynamics simulations, and pharmacokinetic analyses (Zahoor et al., 2024).

This study is to examine the efficacy of the Senggugu plant (*Clerodendrum serratum* (L.) Moon) as a therapeutic agent for diabetes. We conducted the research by simulating the molecular docking of 31 bioactive compounds found

in Senggugu using Molegro Virtual Docker software. The objective was to identify which bioactive compounds in Senggugu have potential antidiabetic activity against five specific protein targets.

Research Methods

Instruments

This research uses tools in the form of computer equipment, a web server, and software. The computer equipment used is an ASUS Vivobook 14X M1403, AMD Ryzen 7 5800H Mobile Processor, Windows 11 Home 64-bit Operating System, 8GB DDR4 RAM, and 512 GB (SSD storage). The software used is Molegro Virtual Docker version 5.0, ChemDraw version 16.0, Discovery Studio Visualizer version 24.1.0.23298, and the web server Protein Data Bank, pkCSM, PubChem, and KNApSAcK family.

Materials

This research uses materials, receptors downloaded from the Protein Data Bank (PDB) (https://www.rcsb.org/), namely human peroxisome proliferator activation gamma (PPRAG) receptor (PDB ID: 7AWC), human dipeptidyl-peptidase-4 (DPP4) receptor (PDB ID: 6Y0F), AKR1C1 receptor (PDB ID: 4YVP), human α-glucosidase receptor (PDB ID: 5NN6), and human (SGLT2) receptor (PDB ID: 7VSI).

Bioactive test ligands and comparator ligands (positive control) were obtained from the PubChem website. Thirty-one test compounds were acquired from the literature search results, along with five comparison compounds.

Procedure

1) Selection and preparation of receptors
   Protein complex structures in (.pdb) format were downloaded from https://www.rcsb.org/. Protein targets were selected based on structure and relevant organisms (Mulatsari et al., 2020). Protein targets downloaded from the Protein Data Bank (PDB) include human peroxisome proliferator activation gamma (PPRAG) receptor (PDB ID: 7AWC) with native ligand Rosiglitazone, human dipeptidyl-peptidase-4 (DPP4) receptor (PDB ID: 6Y0F) with native ligand Linagliptin, AKR1C1 receptor (PDB ID: 4YVP) with native ligand Glibenclamide, human α-glucosidase receptor (PDB ID: 5NN6) with native ligand Miglitol, and human (SGLT2) receptor (PDB ID: 7VSI) with native ligand Empagliflozin. Target proteins were prepared with the Molegro Virtual Docker.
2) Ligand preparation
   The preparation of ligands began with the construction of two-dimensional (2D) structures using Chem2D Professional 16.0, followed by conversion into three-dimensional (3D) structures using ChemDraw 3D 16.0. Subsequently, energy minimization was performed using the MMFF94 force field in Chem3D 16.0 to obtain the most stable (lowest energy) conformation. The optimized structures were then saved in SYBYL (*.mol2) format (Prasetiyo et al., 2024).
3) Validation docking methode
   Validation of the docking protocol was done by redocking each crystal structure with native ligand, including human peroxisome proliferator activation gamma (PPRAG) receptor (PDB ID: 7AWC) with native ligand Rosiglitazone, human dipeptidyl-peptidase-4 (DPP4) receptor (PDB ID: 6Y0F) with native ligand Linagliptin, AKR1C1 receptor (PDB ID: 4YVP) with native ligand Glibenclamide, human α-glucosidase receptor (PDB ID: 5NN6) with native ligand Miglitol, and human (SGLT2) receptor (PDB ID: 7VSI) with native ligand Empagliflozin. Validation was done using Molegro Virtual Docker software. Validation aimed to obtain

the appropriate docking protocol (Siswanto et al., 2019).

4) Molecular docking and visualization
Molecular docking is a computational simulation that models the binding process of a ligand to its receptor. This approach is used to predict interactions between the test ligands and target proteins, as well as to estimate their binding affinity and potential biological activity (Prasetiyo et al., 2019).
Internal validation identified the active binding sites for each receptor as follows: peroxisome proliferator-activated receptor gamma (PPARγ) at coordinates X = 41.43 Å, Y = 5.05 Å, Z = 83.41 Å with a radius of 10 Å; dipeptidyl peptidase-4 (DPP4) at X = 42.08 Å, Y = -72.27 Å, Z = 85.24 Å with a radius of 10 Å; aldo-keto reductase family 1 member C1 (AKR1C1) at X = -74.65 Å, Y = -2.90 Å, Z = -1.20 Å with a radius of 10 Å; α-glucosidase at X = -14.50 Å, Y = -32.20 Å, Z = 95.71 Å with a radius of 10 Å; and sodium-glucose cotransporter-2 (SGLT2) at X = 38.46 Å, Y = 50.43 Å, Z = 46.16 Å with a radius of 10 Å. Molecular docking simulations between the test ligands and each target protein were performed using the Molegro Virtual Docker software. The primary parameter analyzed during docking was the rerank score, which reflects the binding energy between the ligand and the receptor (Saifuddin et al., 2014). The best ligand conformation (pose) was selected based on the lowest binding energy, represented by the most negative rerank score. The optimal docking poses were then visualized using Biovia Discovery Studio (Sari et al., 2020).

5) Drug-likeness and ADMET prediction
Prediction of drug-likeness and ADMET (adsorption, distribution, metabolism, excretion, and toxicity) was done through the pkCSM website. Canonical SMILES of each compound were copied from the PubChem website and then analyzed within the pkCSM website. These were assessed through filters based on Lipinski's rules, including molecular weight, log P, number of hydrogen bond donors, number of hydrogen bond acceptors, etc. After that, the ADMET was predicted (Herdini, 2023; Prasetiyo et al., 2024).

Results and Discussion

Validation of the docking method

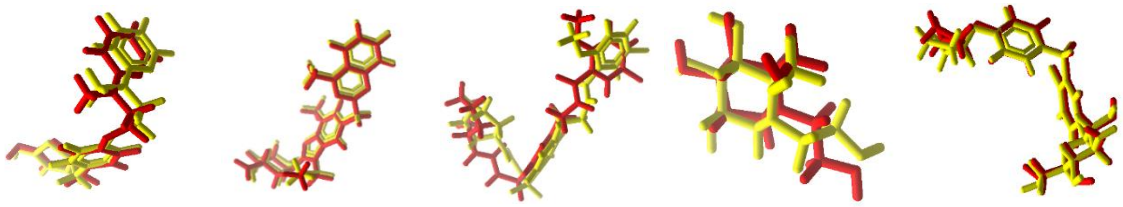
The first stage in the docking process is determining the RMSD (Root Mean Square Deviation) value. RMSD values that are less than or equal to 2 Å indicate that the docking protocol meets the criteria for use, where the shift in the position of the ligand that binds to the protein's active site is not very significant (Mumpuni et al., 2019; Mulyati & Sutjiningtyas, 2022).

Table 1. RMSD value of receptor

No.	PDB Code	Receptor	Resolution (Å)	RMSD Score (Å)
1	7AWC	*peroxisome proliferator activation gamma* (PPRAG)	1,74	0.560044
2	6Y0F	*dipeptidyl-peptidase-4* (DPP4)	2,92	0.443482
3	4YVP	*AKR1C1*	2,60	1.41119
4	5NN6	*α-glucosidase*	2,00	0.600201
5	7VSI	*sodium-glucose cotransporter-2* (SGLT)	2,95	0.407871

Based on Table 1. Receptors that were eligible for use in the docking process of peroxisome proliferator activation gamma (PPRAG) inhibition assay with PDB code ID: 7AWC, dipeptidyl-peptidase-4 (DPP4) with PDB ID code: 6Y0F,

AKR1C1 with PDB ID code: 4YVP, α-glucosidase with PDB ID code: 5NN6, and sodium-glucose cotransporter-2 (SGLT2) with PDB code ID: 7VSI because it has an RMSD value of less than 2 Å. Figure 1 shows the alignment of the native ligand with the redocked native ligand.



(a) (b) (c) (d) (e)

Figure 1. Visualization of protein RMSD **(a)** 7AWC; **(b)** 6Y0F; **(c)** 4YVP; **(d)** 5NN6; **(e)** 7VSI; yellow = native ligand; red = redocked native ligand

Table 2. Rerank score value of the test compound and the comparator

No	Compound	CID	Receptor				
			4YVP	5NN6	7AWC	6Y0F	7VSI
	Comparator compound						
I	Glibenclamide	163079861	-94.8299	-	-	-	-
II	Miglitol	6251	-	-64.7212	-	-	-
III	Rosiglitazone	21594175	-	-	**-105.078**	-	-
IV	Linagliptin	12314864	-	-	-	**-118.803**	-
V	Empaglozin	64945	-	-	-	-	**-135.555**
	Test compound						
1	Beta-amyrenyl acetate	92156	-60.6799	18.4541	102.169	-95.8146	59.9188
2	Lupeol acetate	92157	-70.5297	121.53	105.043	-67.9049	11.9318
3	Epifriedelanol	119242	-67.2614	67.3963	154.009	-77.6476	-13.5091
4	Lupeol	259846	-72.1865	-57.142	77.6904	-75.9536	10.8213
5	Stigmasterol	5280794	**-105.518**	-61.452	-83.4228	-93.057	-112.716
6	Molephantin	5281484	-88.9016	**-73.7913**	-84.9021	-85.2518	-99.3958
7	Molephantinin	5281485	**-106.35**	**-83.9606**	-91.1098	-97.2688	-79.7043
8	Phantomolin	5281493	-90.0764	**-72.6158**	-88.4254	-98.3699	-130.712
9	[(1S,2S,6R,7S,11S)-11-hydroxy-5,9,13-trimethylidene-4-oxo-3,14-dioxatricyclo [9.2.1. 02,6]tetradecan-7-yl] 2-methylprop-2-enoate	9902796	-69.4854	**-68.2228**	-69.4559	-82.4294	-117.503
10	[(3aR,4S,9R,9aR,9bS)-9a-hydroxy-6,9-dimethyl-3-methylidene-2,7-dioxo-3a,4,5,8,9,9b-hexahydro azuleno[4,5-b]furan-4-yl] 2-methylprop-2-enoate	9924324	**-97.1319**	**-68.5755**	-91.2556	-97.5269	-123.679
11	[(3aR,4S,9R,9bS)-9-methyl-3,6-dimethyl idene-2,7-dioxo-3a,4,5,8,9,9b-hexahydro azuleno[4,5-b]furan-4-yl] 2-methylprop-2-enoate	9945304	-94.2922	**-72.5931**	-94.9956	-84.1528	-118.737
12	(4betaH)-5alpha-hydroxy-8alpha-(2-methyl but-2-enoyloxy)-2-oxo-1(10),11(13)-guaiadien-12,6alpha-olide	24814493	**-99.559**	**-77.2044**	-92.3727	-93.3435	-117.874
13	(4betaH)-8alpha-(2-methylbut-2-enoyloxy)-2-oxo-1(5),10(14),11(13)-guaiatrien-12,6alpha-olide	24814494	**-95.5313**	**-83.687**	-92.5152	-94.9827	-123.655
14	[(1S,2S,6R,7S,9Z,11S)-11-methoxy-9,13-dimethyl-5-methylidene-4-oxo-3,14-dioxa tricyclo[9.2.1.02,6] tetradeca-9,12-dien-7-yl] 2-methylprop-2-enoate	73354392	**-106.518**	-64.5399	-87.7565	-90.4038	-99.2953
15	2,5-Epoxy-2beta-hydroxy-8alpha-(2-methylbut-2-enoyloxy)-4(15),10(14),11 (13)-germacratrien-12,6 alpha-olide	86289099	**-95.7842**	**-79.8294**	-76.7747	-88.35	-104.012

No	Compound	CID	Receptor				
			4YVP	5NN6	7AWC	6Y0F	7VSI
16	[3-hydroxy-4-[(2R)-6-methylhept-5-en-2 yl]phenyl] methyl 3-methylbut-2-enoate	92035054	-90.2988	**-87.8719**	-98.6898	-100.761	-113.646
17	[(1S,2S,6R,7S,11R)-11-hydroxy-5,9,13-trimethyl idene-4-oxo-3,14-dioxatricyclo [9.2.1.02,6] tetradecan-7-yl] 2-methylprop-2-enoate	142080342	**-107.663**	**-73.8752**	-76.8358	-86.2988	-109.508
18	[(1R,2S,6R,7S,11S,13R)-11-hydroxy-13-methoxy-13-methyl-5,9-dimethylidene-4-oxo-3,14-dioxatricyclo [9.2.1.02,6] tetradecan-7-yl] 2-methylprop-2-enoate	162872726	-82.1183	**-73.2818**	-63.8804	-91.467	-117.205
19	[(1S,2S,6R,7S,9Z,11R)-11-methoxy-9,13-dimethyl-5-methylidene-4-oxo-3,14-dioxatricyclo[9.2.1.02,6] tetradeca-9,12-dien-7-yl] (E)-2-methylbut-2-enoate	162887887	-72.334	**-72.6423**	-85.6629	-85.8116	-100.013
20	[(3aR,4S,6E,9Z,11S,11aR)-11-hydroxy-6,10-dimethyl-3-methylidene-2,8-dioxo-4,5,11,11a-tetrahydro-3aH-cyclodeca[b] furan-4-yl]2-methylprop-2-enoate	162948442	-80.0733	**-73.9465**	-34.2736	-95.5972	-90.2164
21	[(3aR,4S,6E,9Z,11S,11aR)-11-hydroxy-6,10-dimethyl-3-methylidene-2,8-dioxo-4,5,11,11a-tetrahydro-3aH-cyclodeca[b] furan-4-yl] (E)-2-methylbut-2-enoate	162959520	-79.2389	**-86.6374**	-10.1639	-100.824	-96.0599
22	[(1S,3aR,5aS,7aR,9S,11aR,11bR,13aS,13bR) -3a,5a,8,8,11a,13a-hexamethyl-1-propan-2-yl-1,2,3,4,5,7,7a,9,10,11,11b,12,13,13b-tetradecahydrocyclopenta[a]chrysen-9-yl] acetate	162975981	-78.4517	70.1364	69.159	-82.9433	-61.4115
23	[(1S,2S,6R,7S,9Z,11R)-11-methoxy-9,13-dimethyl-5-methylidene-4-oxo-3,14-dioxatricyclo[9.2.1.02,6] tetradeca-9,12-dien-7-yl] 2-methylprop-2-enoate	163018967	-66.0678	**-69.774**	-80.6277	-80.7512	-99.2195
24	[(1S,2S,6R,7S,11S)-11-hydroxy-5,9,13-trimethyl idene-4-oxo-3,14-dioxatricyclo[9.2.1.02,6] tetradecan-7-yl] (E)-2-methylbut-2-enoate	163029241	-80.2962	**-84.0746**	-71.8375	-85.114	-122.479
25	[(3S,4R,8R,9E,12R,14S)-14-methoxy-10-methyl-5-methylidene-6-oxo-7,13-dioxatricyclo[10.2.1.04,8] pentadeca-1(15),9-dien-3-yl] 2-methylprop-2-enoate	163043788	-90.5177	**-79.3814**	-94.1883	-99.148	-115.26
26	[(1S,2S,6R,7S,9Z,11R)-11-ethoxy-9,13-dimethyl-5-methylidene-4-oxo-3,14-dioxatricyclo[9.2.1.02,6] tetradeca-9,12-dien-7-yl] 2-methylprop-2-enoate	163079861	-72.6065	**-75.621**	-80.9153	-91.2176	-81.3384
27	D-Mannitol	6251	-62.5956	**-71.5622**	-62.346	-57.6475	-69.9371
28	Serratagenic acid	21594175	-46.5234	36.6943	79.1339	-90.3691	-45.6127
29	Queretaroic acid	12314864	-47.4646	68.9138	99.6835	-85.8338	-55.4001
30	Ursolic acid	64945	-41.5692	33.8905	71.6916	-81.9996	35.6777
31	Apigenin-7-glucoside	5280704	**-106.825**	**-75.9439**	-79.8044	-106.321	-125.24

Note: **Bolded** numbers indicate active test compounds compared to comparator compounds, while **purple bolded** numbers indicate the best rerank score for each receptor.

Molecular docking

There are 31 bioactive compounds of senggugu tested for antidiabetic activity against 5 human receptors by the molecular docking method. The 31 compounds were obtained from the Pubchem website, Knapsack Family, and Herdini's research (Herdini, 2023). The Rerank Score values of the tested compounds are shown in Table 2.

Based on the docking results with the Rerank Score value shown in Table 2, it is obtained that the sengugu bioactive compounds that have the best rerank score value (most negative) at the 4YVP receptor are 9 bioactive compounds, and at the 5NN6 receptor are 21 bioactive compounds. The docking results provide different rerank score values because each receptor has different antidiabetic mechanisms for the test compounds and comparator compounds. The compound that has the best rerank score value is a compound that has better selectivity to the receptor. Compared to the comparison compound, test compounds that provide a better rerank score value can be seen from the more negative rerank score value. The more negative the rerank score value, the stronger the bond occurs, so the better the affinity (Prasetiyo et al., 2019).

Table 3. Comparison of the best rerank score value of the Senggugu bioactive compound with the comparator compound

Receptor PDB Code	Compound	Test Compound (Best Score)	Comparator
4YVP	[(1S,2S,6R,7S,11R)-11-hydroxy-5,9,13-trimethylidene-4-oxo-3,14-dioxatricyclo [9.2.1.02,6]tetradecan-7-yl] 2-methylprop-2-enoate	**-107.663**	-94.8299
5NN6	[3-hydroxy-4-[(2R)-6-methylhept-5-en-2-yl]phenyl]methyl 3-methylbut-2-enoate	**-87.8719**	-64.7212
7AWC	[3-hydroxy-4-[(2R)-6-methylhept-5-en-2-yl]phenyl]methyl 3-methylbut-2-enoate	-98.6898	**-105.078**
6Y0F	Apigenin-7-glucoside	-106.321	**-118.803**
7VSI	Phantomolin	-130.712	**-135.555**

Based on Table 3 at the 4YVP receptor, the compound **(17)** [(1S,2S,6R,7S,11R)-11-hydroxy-5,9,13-trimethylidene-4-oxo-3,14-dioxatricyclo[9.2.1.02,6]tetradecan-7-yl] 2-methylprop-2-enoate, which is a bioactive compound of Senggugu gives the best rerank score value of -107.663. The data was compared with the glibenclamide rerank score of -94.8299. Based on the docking score, [(1S,2S,6R,7S,11R)-11-hydroxy-5,9,13-trimethylidene-4-oxo-3,14-dioxa tricyclo [9.2.1.02,6]tetradecan-7-yl] 2-methylprop-2-enoate has better affinity on 4YVP receptor than glibenclamide on the receptor. At receptor 5NN6, the compound **(16)** [3-hydroxy-4-[(2R)-6-methylhept-5-en-2-yl] phenyl]methyl 3-methylbut-2-enoate, which is a bioactive compound of senggugu, gives the best rerank score value of -87.8719. The data was compared with the miglitol rerank score value of -64.7212. Based on the docking score, [3-hydroxy-4-[(2R)-6-methylhept-5-en-2-yl] phenyl] methyl3-methylbut-2-enoate has better affinity for the 5NN6 receptor than miglitol on the receptor.

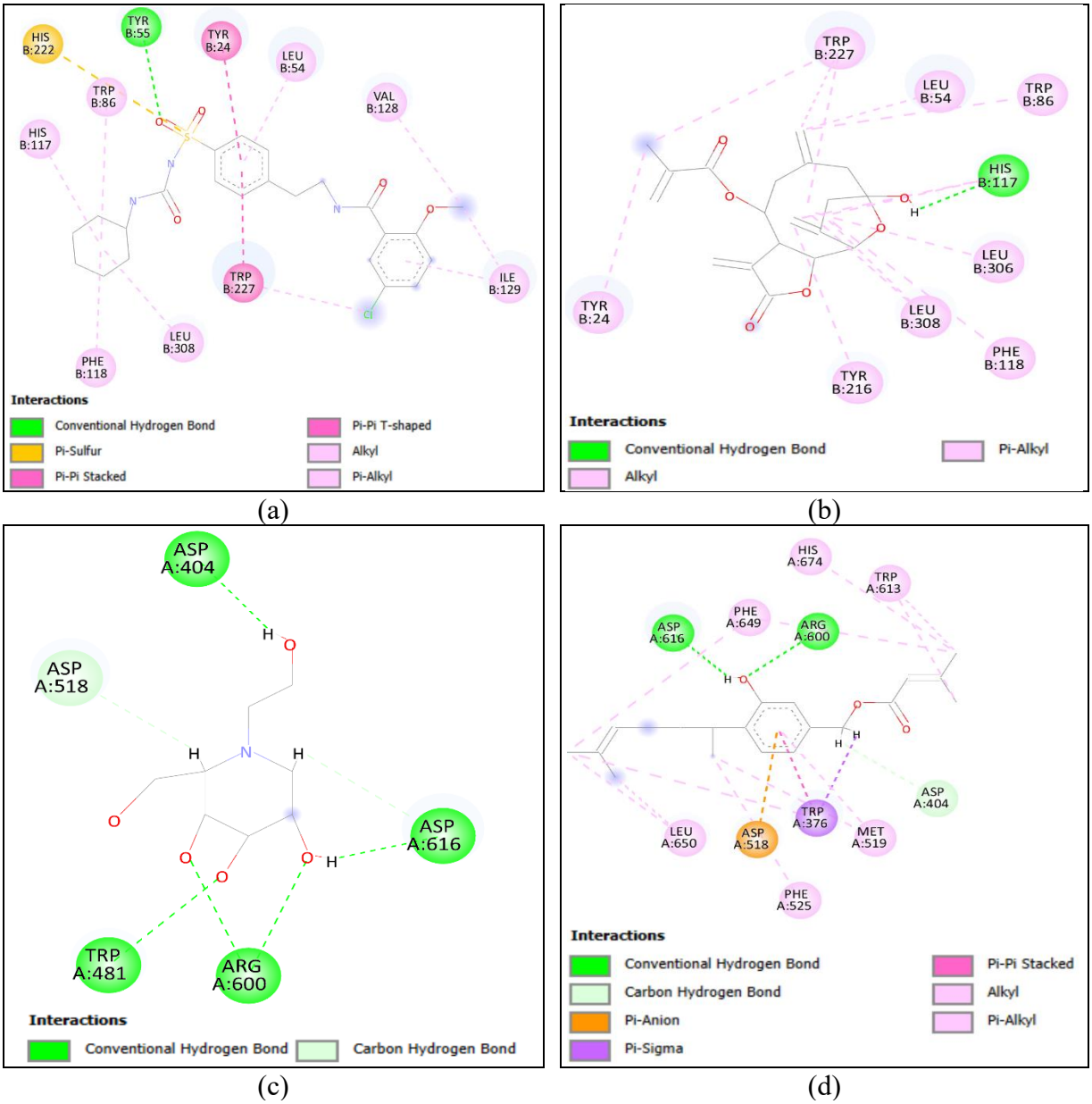


Figure 2. Hydrogen bonding interaction between the ligand and receptor amino acid residues. **(a)** Glibenclamide (4YVP); **(b)** [(1S,2S,6R,7S,11R)-11-hydroxy-5,9,13-trimethylidene-4-oxo-3,14-dioxatricyclo[9.2.1.02,6] tetradecan-7-yl]2-methylprop-2-enoate (4YVP); **(c)** Miglitol (5NN6); **(d)** [3-hydroxy-4-[(2R)-6-methylhept-5-en-2-yl]phenyl]methyl 3-methylbut-2-enoate (5NN6)

The hydrogen bond interactions between the test compounds and the amino acid residues of the receptors are illustrated in Figure 2. In the 4YVP receptor, the reference compound glibenclamide forms hydrogen bonds with the amino acid residue TYR-55. Meanwhile, the test compound [(1S, 2S, 6R, 6R, 7R, 7S, 11R)-11-hydroxy-5,9,13-trimethylene-4-oxo- 3,14-dicyclo [9.2.1.02,6]tetradecan-7-yl] 2-methylprop-2-enoate interacts with the residue HIS-117. Additionally, both glibenclamide and the test compound exhibit interactions with several common amino acid residues, including TYR-24, TRP-86, HIS-117, PHE-118, TRP-227, and LEU-308, indicating overlapping binding profiles. In the 5NN6 receptor, miglitol forms hydrogen bonds with ASP-616, ARG-600, ASP-404, TRP-481, and ASP-518. Similarly, the compound [3-

hydroxy-4-[(2R)-6-methylhept-5-en- 2-yl]phenyl]methyl3-methylbut-2- enoate establishes hydrogen bond interactions with ASP-616, ARG-600, and ASP-404. Both compounds share interaction with similar residues, namely ASP-616, ARG-600, ASP-404, TRP-481, and ASP-518. These docking results suggest favorable binding conformations, supporting the potential of [(1S, 2S, 6R, 6R, 7R, 7S, 11R)-11-hydroxy-5,9,13-trimethylene-4-oxo-3,14-dicyclo [9. 2.1.02,6]tetradecan -7-yl] 2-methylprop-2-enoate and [3-hydroxy-4-[(2R)-6-methyl hept-5-en-2-yl]phenyl]methyl 3-methylbut-2-enoate as potential candidates for the treatment of diabetes mellitus, although the interacting amino acid residues are not completely identical (Yohana, *et al.,* 2024).

Lipinski's Rule of Five

The bioactive compounds in senggugu are expected to function as antidiabetics and have significant biological activity as drugs. Evaluation of the physicochemical properties of ligands is carried out by testing based on the Lipinski criteria, which relate to the absorption and permeability of medications to ensure oral bioavailability. Lipinski's rule that a ligand has a molecular weight (MW) of less than 500 Daltons must have high lipophilicity (the log P partition coefficient value is not more than 5), the number of hydrogen bond donors is not more than 5, and the number of hydrogen bond acceptors is not more than 10 (Lipinski, 2004).

If a compound does not meet the criteria of Lipinski's Rule of Five, it is likely to exhibit issues related to its oral bioavailability. However, compliance with these rules does not guarantee optimal oral activity (Lipinski, 2004). According to Table 4, eleven compounds did not meet Lipinski's criteria: **(1)** β-Amyrenyl acetate, **(2)** Lupeol acetate, **(3)** Epifriedelanol, **(4)** Lupeol, **(5)** Stigmasterol, **(16)** [3-hydroxy-4-[(2R)-6-methylhept-5-en-2-yl] phenyl] methyl3-methylbut-2-enoate, **(22)** [(1S, 3aR,5aS,7aR,9S,11aR, 11bR,13aS,13bR)-3a,5a,8,8,11a,13a-hexamethyl-1-propan-2-yl-1,2,3,4,5,7,7a,9,10,11,11b, 12,13,13b-tetradecahydrocyclopenta[a] chrysen-9-yl] acetate, **(27)** D-Mannitol, **(29)** Queretaroic acid, **(30)** Ursolic acid, and **(31)** Apigenin-7-glucoside.

Nevertheless, other studies suggest that 95% of clinically approved drugs fall within specific physicochemical property ranges: a molecular weight between 130 and 725 g/mol, 0–6 hydrogen bond donors, 2–10 hydrogen bond acceptors, a log P value between –2 and 6.5, and 0–15 rotatable bonds (Chander et al., 2017). Based on these parameters, compounds **(16)** [3-hydroxy-4-[(2R)-6-methylhept-5-en-2-yl] phenyl] methyl3- methylbut-2-enoate, **(29)** Queretaroic acid, and **(31)** Apigenin-7-glucoside may still be considered as potential drug candidates, provided their membrane permeability can be enhanced.

Table 4. Drug-likeness results based on Lipinski's Rule of Five

No. Compound	Parameter				Eligibility
	Molecular Weight (<500 Da)	Log P (<5)	H-Bond Acceptor (<10)	H-Bond Donor (<5)	
1	468.766	**8.7397**	2	0	No
2	468.766	**8.5956**	2	0	No
3	428.745	**8.2488**	1	1	No
4	426.729	**8.0248**	1	1	No
5	412.702	**7.8008**	1	1	No
6	346.379	1.7984	6	1	Yes
7	360.406	2.1885	6	1	Yes
8	374.433	3.0	6	0	Yes
9	346.379	1.9558	6	1	Yes

No. Compound	Parameter				Eligibility
	Molecular Weight (<500 Da)	Log P (<5)	H-Bond Acceptor (<10)	H-Bond Donor (<5)	
10	346.379	1.6323	6	1	Yes
11	328.364	2.4375	5	0	Yes
12	360.406	2.0224	6	1	Yes
13	342.391	2.8276	5	0	Yes
14	360.406	2.6099	6	0	Yes
15	392.448	2.1948	7	1	Yes
16	316.441	**5.2515**	3	1	No
17	346.379	1.9558	6	1	Yes
18	378.421	1.8047	7	1	Yes
19	374.433	3.0	6	0	Yes
20	346.379	1.7984	6	1	Yes
21	360.406	2.1885	6	1	Yes
22	468.766	**8.5956**	2	0	No
23	360.406	2.6099	6	0	Yes
24	360.406	2.3459	6	1	Yes
25	360.406	2.6099	6	0	Yes
26	374.433	3.0	6	0	Yes
27	182.172	**-3.5854**	6	6	No
28	486.693	6.2983	3	3	Yes
29	472.71	**6.206**	3	3	No
30	456.711	**7.0895**	2	2	No
31	432.381	0.0499	10	**6**	No

Note: **Bold** numbers show Lipinski's Rule of Five violated.

ADMET prediction

In new drug development, pharmacokinetic analysis of chemical compounds is essential, covering absorption, distribution, metabolism, excretion, and toxicity before clinical trials. Prediction of ADMET properties is crucial in estimating relevant pharmacokinetic phenomena in drug candidate development (Pratama et al., 2019). Pharmacokinetic and toxicity profiles can be predicted using the pkCSM web server by entering the compound's canonical SMILES.

Table 5. Pharmacokinetic and toxicity profile of test compounds

	Absorption	Distribution			Metabolism				Excretion	Toxicity	
Compound	Intestinal absorption (%)	VDss (log L/kg)	Fraction unbound (human)	BBB permeability (log BB)	CYP2D6 substrate	CYP2D6 inhibitor	CYP3A4 substrate	CYP3A4 inhibitor	Total Clearance (log ml/min/kg)	LD50 (g/kg)	Hepato toxicity
1	97.342	0.1	0	0.634	No	No	Yes	No	-0.134	1134.41	No
2	97.894	-0.12	0	0.644	No	No	Yes	No	0.06	1177.54	No
3	95.938	-0.082	0	0.7	No	No	Yes	No	0.015	1146.89	No
4	95.782	0	0	0.726	No	No	Yes	No	0.153	1093.71	No
5	94.97	0.178	0	0.771	No	No	Yes	No	0.618	1048.26	No
6	98.516	-0.072	0.422	-0.391	No	No	No	No	1.473	824.38	No
7	98.241	-0.11	0.345	-0.382	No	No	No	No	1.511	850.92	No
8	99.879	0.042	0.346	-0.579	No	No	Yes	No	1.339	924.48	No
9	98.072	0.172	0.398	-0.109	No	No	No	No	1.284	796.33	No
10	99.22	-0.008	0.417	-0.446	No	No	No	No	1.259	878.07	No
11	100	-0.106	0.312	-0.311	No	No	Yes	No	0.741	715.51	No
12	99.083	0.021	0.308	-0.369	No	No	No	No	1.295	787.85	No
13	99.163	0.007	0.219	-0.284	No	No	Yes	No	1.34	709.78	No
14	100	0.051	0.357	-0.557	No	No	Yes	No	1.301	889.48	No
15	97.16	-0.042	0.394	-0.61	No	No	Yes	No	1.279	998.78	No
16	91.937	0.248	0.011	0.074	No	No	Yes	No	1.309	733.83	No
17	98.072	0.172	0.398	-0.109	No	No	No	No	1.284	796.33	No
18	97.75	-0.035	0.444	-0.619	No	No	Yes	No	1.237	984.27	No

19	99.531	0.037	0.284	-0.548	No	No	Yes	No	1.341	891.15	No
20	98.516	-0.072	0.422	-0.391	No	No	No	No	1.473	824.38	No
21	98.241	-0.11	0.345	-0.382	No	No	No	No	1.511	850.92	No
22	98.202	0.02	0	0.643	No	No	Yes	No	0.005	1112.85	No
23	100	0.051	0.357	-0.557	No	No	Yes	No	1.301	889.48	No
24	97.483	0.157	0.348	-0.09	No	No	No	No	1.325	808.39	No
25	100	-0.11	0.351	-0.556	No	No	Yes	No	1.345	873.98	No
26	99.879	0.042	0.346	-0.579	No	No	Yes	No	1.339	924.48	No
27	25.401	-0.325	0.868	-1.309	No	No	No	No	0.919	298.22	No
28	66.507	-1.455	0.14	-0.577	No	No	Yes	No	-0.077	1196.78	No
29	100	-1.233	0.029	-0.412	No	No	Yes	No	0.026	1133.09	Yes
30	100	-1.088	0	-0.141	No	No	Yes	No	0.083	1071.44	Yes
31	37.609	0.342	0.218	-1.391	No	No	No	No	0.547	1122.03	No

The parameter used in the absorption profile analysis (Table 5) is the HIA value. HIA (human intestinal absorption) relates to the ability of the intestine to absorb the drug from an orally administered solution. HIA values ranging from 0 to 20% indicate that the compound's absorption is less effective, while HIA values between 20 and 70% indicate a moderate absorption level. On the other hand, HIA values that reach 70 to 100% indicate that the compound has a reasonable absorption rate (Az-Zahra et al., 2022). Of the 31 compounds tested, three compounds were found to have moderate absorption, including **(31)** apigenin-7-glucoside, **(27)** D-mannitol, and **(28)** Serratagenic acid, while the other 28 compounds had good absorption.

The distribution profile was viewed from the VDss (volume distribution at steady state), BBB permeability, and unbound fraction values (Table 5). The drug distribution profile was predicted using the pkCSM web. The volume of distribution (VD) describes the drug dose required to reach a plasma concentration. High VDss indicates more distribution to tissues, while VDss is low if Log VD < -0.15 and high if Log VD > 0.45 (Hardjono, 2017). The predicted VDss values of the test compounds are -1.455 to 0.248, where 5 test ligands have VD values < -0.15, so it can be expected that almost all test ligands can be evenly distributed in providing the same concentration.

BBB (blood-brain barrier) is the ability of a drug to cross the brain barrier, which is an essential factor in reducing side effects and toxicity while increasing the effectiveness of drugs that have pharmacological activity in the brain. A compound can penetrate the brain barrier well if its log BB value is > 0.3, while the compound cannot be distributed well if its log BB value is < -1 (Kadry et al., 2020). In this case, the compound should not penetrate the BBB because the compound is not intended for the nervous system. Based on table 5, the log BB values of the test ligands ranged from -1.391 to 0.771, which indicates that six compounds, namely **(1)** beta-amyrenyl acetate, **(2)** lupeol acetate, **(3)** epifriedelanol, **(4)** lupeol, **(5)** stigmasterol, and **(22)** [(1S,3aR,5aS,7aR, 9S,11aR,11bR,13aS,13bR)-3a, 5a,8,8,11a, 13a-hexamethyl-1-propan -2-yl-1,2,3,4,5,7, 7a,9,10,11,11b,12, 13,13b-tetradecahydro cyclopenta[a] chrysen-9-yl] acetate could penetrate the BBB, while the other 25 compounds could not. Most drugs in plasma are balanced between bound and unbound plasma proteins. The effectiveness of drug delivery can be affected by this condition. The more a drug is bound to proteins in the blood, the lower the efficiency of the drug in penetrating the cell membrane (Prasetiyo et al., 2024). The predicted unbound fraction values of the test compounds were 0 to 0.868, indicating most of the compounds were eligible.

Cytochrome P450 is a key enzyme in the detoxification process found in the liver. These enzymes function by oxidizing foreign organic compounds,

including drugs, and assisting in excreting these compounds from the body (Syarif, 2023). It is therefore important to assess the ability of compounds to inhibit cytochrome P450, which in this study is represented by cytochrome isoforms CYP2D6 and CYP3A4. From Table 5, it can be seen that all test ligands affect or inhibit these enzymes.

A compound's excretion profile can be determined by measuring total clearance. Total clearance is the result of a combination of clearance that occurs in the kidney and clearance that takes place in the liver. The total clearance value is closely related to the drug's bioavailability and establishes the dose required to achieve the desired concentration (Abdullah et al., 2021). Excretion values of the test compounds were predicted, ranging from -0.134 to 1.511 log ml/min/kg.

Toxicity estimation based on LD50 (Lethal Dose 50) values relates to the single amount of a substance that can result in death in 50% of the test animal population. A higher LD50 value indicates that the tested substance has a better safety level (Hardjono, 2017). The estimated LD50 values of the test compounds ranged from 298.22 to 1196.78 g/kg, indicating that the bioactive compounds in senguggu belonged to toxicity level 6, which means harmless (>15 g/kg).

Conclusions

Active compounds derived from *Senggugu* (*Clerodendrum serratum*) predicted to exhibit effective antidiabetic activity based on molecular docking results, Lipinski's rule of five, and pharmacokinetic prediction analyses include [3-hydroxy-4-[(2R)-6-methylhept-5-en-2-yl] phenyl] methyl3-methylbut-2-enoate (–87.8719 kcal/mol) and [(1S,2S,6R,7R,11R)-11-hydroxy-5,9,13-trimethylena-4-oxo- 3,14-dioxocyclo [9.2.1.02,6]tetradecan-7-yl] 2-methylprop-2-enoate (–107.663 kcal/mol). These compounds demonstrate strong potential for further development through chemical synthesis and evaluation in *in vitro* and *in vivo* studies as antidiabetic agents.

Author Contributions

YTR and EM* contributed to the conceptualization of the research. YTR, EM*, and AP designed the methodology. YTR and AP run the research using computational software. YTR, EM*, and EM conducted the research validation. YTR performed the formal analysis, investigation, data visualization, and project administration. YTR, IAT, MD, AM prepared the resources. YTR and EM* handled the data curation. YTR, IAT, MD, AM, ES, and JDS wrote the original manuscript draft. YTR and EM* reviewed and edited the manuscript. EM*, AP, and EM had responsibility for the research supervision. EM* prepared for the funding acquisition. All authors contributed and agreed to the final version of the manuscript.

Conflict of Interest

The authors have declared that there is no conflict of interest.

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