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Email : editorijhess@gmail.com

Design of New Antidiabetic Compounds Using Structure-Based Drug Design Method on Kaempferol Derivatives from Guava Leaves (Psidium guajava L.)

Nadine Aurelia Hasugian[1)], Tiara Ajeng Litsyani[2)], Danang Raharjo[3)]
[1,2,3)]Bachelor of Pharmacy Study Program, Faculty of Health Sciences, Duta Bangsa University, Surakarta

*Corresponding Author
Email : nadinehasugian53@gmail.com

Abstract

Diabetes mellitus is a chronic metabolic disorder with increasing global prevalence, requiring new antidiabetic candidates to inhibit α-amylase and α-glucosidase enzymes to control postprandial glucose. This study aims to design kaempferol derivative compounds from guava leaves (Psidium guajava L.) through Structure-Based Drug Design in silico. This type of computational experimental study uses 15 ligands as purposive samples from the population of flavonoid compounds and target enzymes. Instruments include ChemDraw, PyRx-AutoDock Vina, Swiss ADME, Toxtree, and Discovery Studio, with analysis of binding free energy (ΔG), RMSD, and ADME-toxicity prediction. The results showed that the new compound 4-(2-hydroxy-1-(hydroxymethoxy butyl)cyclohexan-1-ol has a ΔG of -5.5 kcal/mol (α-amylase) and -5.9 kcal/mol (α-glucosidase), RMSD <2 Å, fulfills Lipinski's rule, and has low toxicity (Low Class I). The conclusion states that this compound has the potential as a safe antidiabetic candidate with implications for the development of local flavonoid-based drugs.

Keywords: Alpha-Amylase, Alpha-Glucosidase, Antidiabetic, Drug Design, Kaempferol

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia due to insulin deficiency or dysfunction, leading to an increasing global prevalence. In 2021, approximately 537 million adults aged 20–79 years were living with DM, with the number projected to reach 783 million by 2045, primarily in middle-income countries.

Complications of uncontrolled diabetes include neuropathy, nephropathy, retinopathy, and cardiovascular disease, making postprandial blood glucose control crucial for preventing morbidity and mortality. This prevalence continues to increase, with the International Diabetes Federation (2021) estimating a significant increase in urban areas compared to rural areas, underscoring the need for effective therapeutic interventions.

A major challenge in the management of diabetes is the postprandial glucose spike caused by the activity of carbohydrate-digesting enzymes such as α-amylase and α-glucosidase, which break down polysaccharides into readily absorbable glucose. Inhibiting these enzymes can slow glucose absorption, reducing postprandial hyperglycemia, as supported by recent studies. However, conventional drugs such as acarbose often cause gastrointestinal side effects, necessitating the need for new, safer candidates.

Guava leaves (Psidium guajava L.) have traditionally been used as an antidiabetic agent due to their flavonoid content, such as kaempferol, which has the potential to inhibit these enzymes through antioxidant and glucose-regulating activities. Phytochemical studies indicate that bioactive compounds from P. guajava, including flavonoids and phenolics, contribute to its antidiabetic effects, but structural optimization is needed to improve efficacy. However, the lack of derived compounds that have been evaluated in silico has limited the development of natural-based drugs.

Structure-Based Drug Design (SBDD) approach through molecular docking allows modification of kaempferol structure to increase affinity to the active site of α-amylase and α-glucosidase, with better ADME and toxicity prediction compared to the parent compound. This study aims to design new compounds derived from kaempferol from guava leaves using SBDD in silico, evaluate the enzyme inhibition potential, and predict its pharmacokinetic and safety profiles. The urgency of this study lies in the need for new safe and effective antidiabetic candidates amidst the

soaring prevalence of DM, while the novelty lies in the design of a specific compound 4-(2-hydroxy-1-hydroxymethoxybutylcyclohexan-1-ol that meets Lipinski's rule with low toxicity (Low Class I) and competitive binding affinity.

RESEARCH METHODS

This study uses a computational experimental research type with a Structure-Based Drug Design (SBDD) approach that focuses on the design of new compounds derived from kaempferol from guava leaves (Psidium guajava L.) as antidiabetic candidates through in silico simulations. This approach involves ligand structure modification, molecular docking with α-amylase and α-glucosidase enzymes, and pharmacokinetic and toxicity evaluations, which are aligned with computational quantitative research methods to optimize binding affinity and predict biological activity. Sugiyono (2021) emphasizes that this type of experimental method is effective for hypothesis testing through controlled manipulation of variables in a virtual environment, while Creswell and Creswell (2018, latest edition accessed 2024) support the integration of a mixed methods computational approach for the validation of structural predictions.

The main instruments include software such as ChemDraw Ultra 22.0 and Chem3D Ultra 22.0 for the generation and optimization of 3D ligand structures, PyRx 0.8 with AutoDock Vina for molecular docking, SwissADME for ADME prediction, Toxtree for toxicity analysis, and Discovery Studio Visualizer for interaction visualization. Data analysis techniques include the calculation of binding free energy (ΔG), Root Mean Square Deviation (RMSD) for docking validation (with a threshold of <2 Å), the application of Lipinski's rule for drug-likeness properties, and the prediction of gastrointestinal absorption and CYP inhibition. Emzir (2020) underlines the importance of computational instruments in qualitative-structural data analysis to ensure reliability, while Sudaryono (2022) highlights the use of docking software as a high-precision quantitative technique in computational pharmaceutical research.

The population in this study consisted of the flavonoid kaempferol derivative compound from guava leaves along with the target enzymes α-amylase (PDB ID: relevant) and α-glucosidase, with a purposive sample of 15 structurally modified ligands selected based on their carbohydrase inhibition potential. This sample selection was based on the bioactive characteristics of flavonoids known to inhibit glucose-digesting enzymes, including the new compound 4-(2-hydroxy-1-hydroxymethoxybutyl)cyclohexan-1-ol as the main focus compared to the controls kaempferol and acarbose. Sugiyono (2019) recommends purposive sampling for experimental research to ensure representation of virtual population characteristics, while Creswell (2024 edition) adds that in computational design, samples are limited to relevant molecular entities for analysis efficiency.

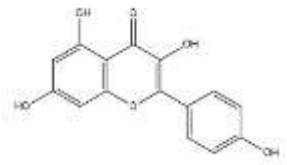
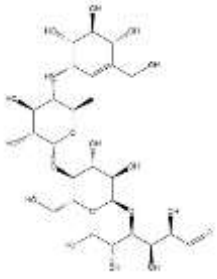
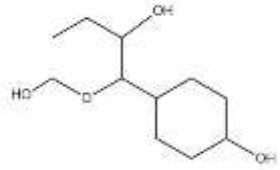
The procedure begins with the creation of a 2D ligand structure using ChemDraw, conversion to 3D via Chem3D, and optimization with VegaZZ; followed by macromolecule preparation through separation of native ligands and residual water in Discovery Studio. [Listyani et al., 2018] Docking validation is carried out via redocking of native ligands to confirm RMSD, then the main docking process in PyRx with a grid box on the enzyme active site, residue interaction analysis, ADME prediction in SwissADME, and toxicity in Toxtree. [Amrulloh et al., 2023] Emzir (2019) and Sugiyono (2022) emphasize this systematic sequence of procedures to maintain the validity of computational data, with Sudaryono (2021) supporting docking iteration as a crucial step in in silico drug development.

RESULTS AND DISCUSSION

Drug design is an iterative process that begins with the identification of compounds that exhibit important biological properties and ends with optimization steps, both in terms of activity profiles and chemical compound synthesis. Drug design is generally based on structural similarity testing and the differentiation between active and inactive molecules. Drug design encompasses not only ligand design but also pharmacokinetics and toxicity, which are generally beyond the capabilities of computer-aided design (Wardani & Listyani, 2024).

The structural design of the new compound was created using the ChemDraw 2D application. The new compound was created by reducing the benzene chain and hydroxyl (OH) group from the starting compound. In computationally designing new compounds with desired activity, the hydroxyl group is one of the substructures that can be generated from a known compound (Takeda et al., 2019).

Table 1.

Kaempferol	**Acarbose**	**New Compound** (*4-(2-hydroxy-1-(hydroxymethoxy)butyl)cyclohexan-1-ol*)
		

The structural name of the new compound was determined by selecting the Structure menu and then clicking Convert structure to name. This resulted in the structural name of the new compound design, 4-(2-hydroxy-1-(hydroxymethoxy)butyl)cyclohexan-1-ol. The structure of the new compound was then converted into 3D format using Chem3D and optimized using the VegaZZ program. The new compound was then docked with α-amylase and α-glucosidase macromolecules, then amino acid residues were analyzed using the Discovery Studio Visualizer application, and toxicity and ADME parameter tests were performed (Wardani & Listyani, 2024).

Table 2.

Parameter	**Molecule**					
	Kaempferol		**Acarbose**		**New Compound**	
	a-amylase	***a-glucosidase***	***a-amylase***	***a-glucosidase***	***a-amylase***	***a-glucosidase***
(kcal/mol)	-7.9	-6.5	-7.4	-6.9	-5.5	-5.9
RMSD	1,378	1,579	1.99	2,277	1,589	1,263
Amino Acid Residues	ASPA: 197, GLUA: 233	LEU A: 868	ASPA: 402, ASNA: 5	VAL A: 375, VAL A: 867, GLU A: 869	ASPA: 300	HISA: 584

Molecular Weight (g/mol)	286.24	645.60	218.29
H-Bond Acceptor	6	19	4
H-Bond Donor	4	14	3
LogP	1.58	-6.24	0.95
Solubility in Water	Late	Late	Late
GI Absorption	High	Low	High
BBB Permeant	No	No	No
Pgp Substrate	No	Yes	No
CYP1A2 Inhibitor	Yes	No	No
CYP2C19 Inhibitor	No	No	No
CYP2C9 Inhibitor	No	No	No
CYP2D6 Inhibitor	Yes	No	No
CYP3A4 Inhibitor	Yes	No	No
Cramer Rules Toxicity Test	*High Class III*	*High Class III*	*Low Class I*
Toxicity, Carcinogenicity, and Mutagenicity Tests	*Negative for Genotoxic Carcinogenicity, Negative for Nongenotoxic Carcinogenicity*	*Structural Alert for Genotoxic Carcinogenicity, Negative for Genotoxic Carcinogenicity*	*Negative for Genotoxic Carcinogenicity, Negative for Nongenotoxic Carcinogenicity*
In-Vitro Mutagenicity Toxicity Test	*No Alert fo S. Typhimurium Mutagenicity*	*Structural Alert for S. Typhimurium Mutagenicity*	*No Alert fo S. Typhimurium Mutagenicity*

After modifying the design of the new compound on the kaempferol compound with the reference compound acarbose to produce a new compound 4-(2-hydroxy-1-(hydroxymethoxy)butyl)cyclohexan-1-ol, the results of the modification of the new compound design were quite good. For the docking results on the new compound, the results showed a decrease in ΔGbind a-amylase from -7.9 kcal/mol to -5.5 kcal/mol and ΔGbind a-glucosidase from -6.5 kcal/mol to -5.9 kcal/mol. The new compound has good physicochemical parameters (MW 218.29 g/mol, logP 0.95), so that GI absorption is high, the molecular size is small and the lipophilicity is moderate. The ADME prediction results are in accordance with the Lipinski criteria.

The Cramer toxicity test showed that kaempferol and acarbose were in High Class III, meaning they have complex chemical structures and higher toxicity potential compared to the new compounds. The toxicity prediction results showed that the new compounds were not toxic (low class I), carcinogenic, or mutagenic.

This indicates that the newly designed compound exhibits interactions similar to the native ligand, as well as good ADME activity and low toxicity. Based on these results, it can be concluded that this new compound has potential as an antidiabetic agent against the α-amylase and α-glucosidase enzyme receptors.

CONCLUSION

This study successfully designed a new compound 4-(2-hydroxy-1-(hydroxymethoxy butyl) cyclohexan-1-ol from guava leaf kaempferol derivative (Psidium guajava L.) through Structure-Based Drug Design in silico approach, which showed strong antidiabetic potential with competitive binding affinity to α-amylase (ΔG -5.5 kcal/mol) and α-glucosidase (ΔG -5.9 kcal/mol) enzymes, as well as RMSD below 2 Å confirming the validity of the interaction. This compound meets Lipinski's rules with a molecular weight of 218.29 g/mol, LogP 0.95, high gastrointestinal absorption, and low toxicity (Low Class I Cramer Rules), superior to kaempferol and acarbose in terms of safety and pharmacokinetic profiles. These findings confirm that simple structural modifications can enhance the efficacy of carbohydrate-digesting enzyme inhibition, potentially suppressing postprandial glucose spikes in people with diabetes mellitus. This research is limited by the in silico nature of predictions that have not been validated in vitro or in vivo, potential bias from docking software, and the lack of physical synthesis data for the compounds. Suggestions for further research include empirical biological testing, further optimization with machine learning, and cross-disciplinary collaboration for clinical drug development. Practically, these results provide implications for the Indonesian pharmaceutical industry in developing safe and affordable local flavonoid-based antidiabetic supplements to support diabetes control in a country with a high prevalence like Indonesia.

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