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Design Of New Compounds Derived From Rosella Flavonoids As Diabetes Mellitus Enzyme Inhibitors Using Computer-Aided Drug Design Strategy

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Abstract

Type 2 diabetes mellitus is increasing rapidly in Indonesia with a projected prevalence of 16.09% in 2045, requiring local plant-based α-amylase and α-glucosidase enzyme inhibitors such as the flavonoid kaempferol-3-O-rutinoside from roselle flowers (Hibiscus sabdariffa L.), which shows potential in silico inhibition but suboptimal ADMETox profile. This in silico computational experimental study aims to design kaempferol-3-O-rutinoside derivative compounds as effective inhibitors through computer-aided drug design, with a population of parent compounds, target enzymes, and acarbose as controls; purposive samples in the form of substituent modifications; PyRx-AutoDock Vina, SwissADME, Toxtree instruments; and molecular docking analysis techniques (ΔG, RMSD) and ADMETox prediction. The results showed a new compound with ΔGbind -5.0 kcal/mol (α-amylase, RMSD 1.538), -5.2 kcal/mol (α-glucosidase, RMSD 2.08), similarity of residues Asn A 570, Asp A 243, Val A 867, high GI absorption (molecular weight 340.41 g/mol, LogP 0.06), and low class I toxicity. In conclusion, the new compound has the potential as a safe oral antidiabetic drug candidate, in vitro/in vivo validation is recommended for further development.

Keywords: Alpha-Amylase, Alpha-Glucosidase, Computer-Aided Drug Design, Molecular Docking, Rosella Flavonoids

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia due to abnormalities in insulin secretion, insulin action, or both, which can lead to chronic complications affecting the eyes, kidneys, nerves, and blood vessels. Globally, the prevalence of DM in adults increased from 7% to 14% between 1990 and 2022, with more than 800 million cases expected by 2024, with the majority of untreated cases occurring in low- and middle-income countries. In Indonesia, the prevalence of DM is estimated to rise from 9.19% in 2020 to 16.09% in 2045, representing a 75.1% increase with an average annual growth rate of 3%, particularly in the Java-Bali region.

The empirical use of roselle flowers (Hibiscus sabdariffa L.) by Indonesians as an antidiabetic agent is supported by its main flavonoid content, such as kaempferol-3-O-rutinoside, which exhibits inhibitory activity against diabetes enzymes. Flavonoids from roselle have the potential to inhibit carbohydrate digestive enzymes such as α-amylase and α-glucosidase, thereby reducing postprandial glucose absorption.

Despite this, the prevalence of type 2 diabetes mellitus (DM) in Indonesia continues to increase significantly, with a projected 40.7 million cases by 2045, accompanied by a sharp increase in complications such as neuropathy and retinopathy. Key risk factors include obesity, hypertension, low physical activity, and high sugar consumption, which exacerbate chronic hyperglycemia and burden the national health system.

Inhibition of α-amylase and α-glucosidase enzymes is the main strategy for post-meal blood glucose control, where α-amylase breaks down polysaccharides into oligosaccharides and α-glucosidase hydrolyzes them into glucose that is easily absorbed by the intestine. However, roselle flavonoid compounds such as kaempferol-3-O-rutinoside show good inhibitory activity against both enzymes in silico, but their ADMETox profile is still less than optimal for drug development.

Conventional treatments such as acarbose often cause gastrointestinal side effects, necessitating the need for natural inhibitors with better pharmacokinetic profiles. The design of new

compounds derived from roselle flavonoids is needed to improve binding affinity, binding free energy, and predict ADME and reduce toxicity.

This study aims to design a new compound derived from kaempferol-3-O-rutinoside from roselle flavonoids as an α-amylase and α-glucosidase inhibitor through a computer-aided drug design (CADD) approach, including molecular docking, ADMETox prediction, and interaction analysis. The urgency of the research arises from the increasing cases of DM in Indonesia which requires local plant-based oral antidiabetic drug candidates with a safe profile, considering the projected 16.09% prevalence in 2045. The novelty of the study lies in the modification of the structure of the roselle compound to achieve low RMSD, optimal ΔG bind, and superior ADMETox compared to its parent, opening up opportunities for the development of new drugs based on SBDD.

RESEARCH METHODS

This research is a computational experimental study aimed at designing new compounds derived from roselle (Hibiscus sabdariffa L.) flavonoids as inhibitors of diabetes mellitus enzymes through a computer-aided drug design (CADD) strategy, focusing on molecular docking, ADME prediction, and toxicity. This approach is categorized as an experimental in silico study because it involves virtual manipulation of molecular structures to observe interactions and changes in pharmacokinetic and toxicological properties after compound modification. Sugiyono (2021) explains that computational experimental methods such as this are suitable for hypothesis testing at the molecular level without the need for physical samples, while Sudaryono (2021) emphasizes the integration of quantitative approaches in numerical data analysis such as binding energies.

The main instruments used include software such as PyRx with AutoDock Vina for molecular docking, SwissADME for ADME prediction, Toxtree for toxicity analysis, and visualization tools such as Discovery Studio Visualizer, ChemDraw, and Vega ZZ. Data analysis techniques include calculating binding free energy (ΔG), RMSD, visualization of amino acid residue interactions, and evaluating ADMETox parameters based on Lipinski and Cramer's rules. Emzir (2021) supports the use of computational software as a primary instrument in quantitative pharmaceutical research for the validation of ligand-protein interactions, while Creswell and Creswell (2023) in a recent edition highlight data triangulation from multiple tools to improve the reliability of mixed-method in silico analysis.

The population in this study consisted of the main flavonoid compound from roselle flowers, namely kaempferol-3-O-rutinoside, along with the target enzymes α-amylase (related GDP ID) and α-glucosidase, with acarbose as a positive control. Samples were selected by purposive sampling, namely the design of new compounds modified from kaempferol-3-O-rutinoside with optimal substituents to improve binding affinity and ADMETox profiles. Sugiyono (2021) stated that purposive sampling is ideal for experimental research limited to specific molecular entities, while Sudaryono (2021) added that the size of such virtual samples is determined by structural relevance to the biological target.

The procedure begins with macromolecule preparation by separating ligands and water using Discovery Studio Visualizer, followed by ligand optimization by hydrogen addition and energy minimization in Vega ZZ. Molecular docking was then performed via PyRx-AutoDock Vina to calculate ΔG and RMSD, and ADME prediction using SwissADME (**http://www.swissadme.ch**), and toxicity with Toxtree based on a decision tree. New compound design analysis involves modifying the R substituent to match residue interactions with acarbose, validated through data visualization and comparison. Creswell and Creswell (2023) describe this stepwise procedure as a systematic sequential explanatory design, supported by Emzir (2021) for its logical sequence from preparation to in silico validation.

RESULTS AND DISCUSSION

New compound design is the process of designing or modifying the chemical structure of a ligand to have optimal affinity and interaction with a specific protein target (e.g., a receptor or enzyme), thereby maximizing its biological potential as a drug candidate. New compound design functions as part of structure-based drug design (SBDD), where three-dimensional information from the protein target is used to predict the ligand binding mode and select substituents that can enhance important interactions such as hydrogen bonds or hydrophobic interactions. This study provides the additional benefit of generating hypotheses about the biological mechanisms of drugs or diseases in the process of discovering new drug candidates. Research conducted showed that the flavonoid compound kaemferol-3-0-rutinoside has good activity against α-amylase and α-glucosidase inhibitors in inhibiting antidiabetic inhibitory enzymes but has poor ADME/Tox properties. The new compound design table can be seen in Table 1, and the docking results table, toxicity test and ADME test of the new compound design can be seen in Table 2.

Table 1. New Compound Design

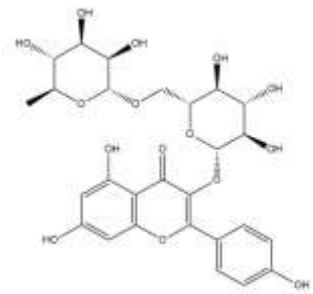
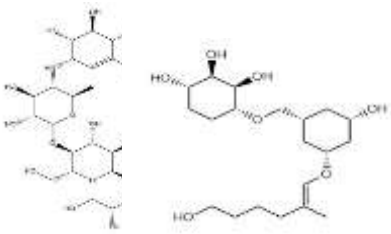
Kaempferol-3-rutinoside	**Acarbose**	**New Compound** (2R,3R,4S,5S)-2,3,4-trihydroxycyclohexyl O-[(2R,3S)-3-hydroxycyclohexyl] O-[4-hydroxyhex-1-en-2-yl] ether
		

Table 2. Docking results, toxicity test and ADME test of new compound design

Parameter	Molecule					
	Kaempferol 3 rutinoside		Acarbose		New Compound	
	a-amylase	a-glucosidase	a-amylase	a-glucosidase	a-amylase	a-glucosidase
(kcal/mol)	-8.9	-7.4	-7.4	-6.9	-5.0	-5.2
RMSD	1,083	2,070	1.99	2,277	1,538	2.08
Amino Acid Residues	GLUA: 233, ASPA: 300	GLU A: 866, HIS A: 584	ASP A: 402, ASN A: 5	VAL A: 375, VAL A: 867, GLUA: 869	ASP A: 243, ASN A: 570	VAL A: 867
Molecular Weight (g/mol)	594.52		645.60		340.41	
H-Bond Acceptor	15		19		8	
H-Bond Donor	9		14		4	
LogP	1.64		-6.24		0.06	
Solubility in Water	Late		Late		Late	
GI Absorption	Low		Low		High	
BBB Permeant	No		No		No	
Pgp Substrate	Yes		Yes		Yes	
CYP1A2 Inhibitor	No		No		No	
CYP2C19 Inhibitor	No		No		No	
CYP2C9 Inhibitor	No		No		No	
CYP2D6 Inhibitor	No		No		No	
CYP3A4 Inhibitor	No		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	

Based on the results of the modification of the new compound, the docking results for the α-amylase enzyme were ΔGbind 5.0 kcal/mol, while the docking results for α-glucosidase were ΔGbind 5.2 kcal/mol. The amino acid residues of the new compound design with the α-amylase enzyme are similar to the positive control (acarbose), namely the amino acids Asn A: 570 and Asp A: 197. While the new compound with the α-glucosidase enzyme has the same amino acid residue, namely VAL A: 867. This shows that the new compound design is effective as an α-amylase and α-glucosidase inhibitor.

The ADME test results on the new compound showed a significant change, namely in GI Absorption to high, this compound has the potential to be a drug candidate. The results of the toxicity test on this new compound showed a significant change, namely in the level of toxicity with the Cramer Rules parameter where the new compound became low class, as well as changes in the in vitro mutagenicity parameter (Amest test) alerts by ISS, it was known that the new compound was No Alert

fo S. Typhimurium Mutagenicit. This shows that the design of the new compound is more effective as a candidate for a new drug candidate for α-amylase and α-glucosidase inhibitors.

CONCLUSION

The conclusion of this study confirms that the design of a new compound derived from kaempferol-3-O-rutinoside from roselle flavonoids (Hibiscus sabdariffa L.) successfully produced an effective inhibitor candidate against the enzymes α-amylase (ΔGbind -5.0 kcal/mol, RMSD 1.538) and α-glucosidase (ΔGbind -5.2 kcal/mol, RMSD 2.08), with similar interaction residues such as Asn A 570, Asp A 243, and Val A 867 to the acarbose control. Significant improvements were seen in the ADMETox profile, where GI absorption increased to high, Cramer Rules toxicity decreased to low class I, and there was no in vitro mutagenicity alert, fulfilling Lipinski's rules for the development of oral antidiabetic drugs. These findings support the potential of roselle compounds as a natural alternative treatment for type 2 diabetes mellitus, considering the high prevalence in Indonesia. This study relies on a purely in silico approach without in vitro or in vivo experimental validation. Therefore, the docking and ADMETox prediction results require empirical confirmation to ensure bioavailability and clinical efficacy. Suggestions for further research include chemical synthesis of new compounds, enzymatic testing, and preclinical studies in diabetic animal models. Practically, these results have implications for the development of local roselle-based antidiabetic supplements, reducing dependence on conventional drugs such as acarbose, which have gastrointestinal side effects, and contributing to postprandial hyperglycemia control strategies in developing countries.

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