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In Silico Screening of Brotowali (*Tinospora crispa* l.) Chemical Compounds as α-Glucosidase Inhibitor Using the Pyrx Program

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Abstract. This study aims to determine the chemical compound of brotowali (*Tinospora crispa* L.)which has the potential as an α-glucosidase inhibitor *in silico.*The method employed was *Molecular docking* with the PyRx program. Theα-glucosidase enzyme model as receptor was downloaded from the Protein Data Bank (PDB) database with the code of 1LWJ while the chemical compound model as a test ligand was retrieved from the Zinc and *KNApSAcK* databases with positive control of acarbose. The validation of the *docking* method showed an RMSD value of 0.901Å. The findings showed that the 35 chemical compounds from brotowali (*Tinospora crispa* L.)had a bond-free energy value(ΔG)ranging from-5.2 kcal/mol to -11.6 kcal/mol. 4 potential chemical compounds to be developed as α-glucosidase inhibitors with ΔGbetter than acacia (ΔG-9.8kcal/mol), namelyN-acetylanonaine (-11.6 kcal/mol), Stigmasterol (-10.7kcal/mol), N-Formylanonaine (-10.6 kcal/mol),and Berberine (-10.3 kcal/mol).

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia due to abnormalities in insulin secretion, insulin action, or both. DM is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use its insulin function [1].

Oral treatment for DM patients is to inhibit the action of the α-glucosidase enzyme, which plays a role in the conversion of carbohydrates into glucose. The α-glucosidase inhibitor compounds work to inhibit the α-glucosidase enzyme found in the small intestine. Inhibition of the α-glucosidase enzyme can effectively reduce the digestion and absorption of complex carbohydrates, thereby reducing the increase in postprandial glucose levels in DM patients. Therefore, inhibition of the α-glucosidase enzyme allows blood glucose levels to return to normal limits [2].

Indonesia is a tropical country that has many types of plants. There are many medicinal plants reported to be useful and used as antidiabetic agents empirically. The compound content in plants is reported to be safe for diabetics [3]. One of the medicinal plants that has attracted a lot of attention in recent years is brotowali (*Tinospora crispa* L.) which has traditionally been used by the Indonesian people (Borneo) in the treatment of diabetes [4]. A study [2] on the measurement of α-glucosidase enzyme inhibition activity carried out in Vitro has proven that simplicia-solvent ratio, brotowali ethanol extract with a ratio of 1:10 has α-glucosidase enzyme inhibition of 81.31%. The main components that have been identified as active are terpenoids and terpenoid glycosides. The terpenoid glycosides that play a role in lowering blood sugar serum in type 2 diabetes patients are borapetoside C and borapetols B [2].

Computational methods and applications in the field of pharmacy has evolved over the last few decades to answer the need to understand molecular biology structure and discover new structural-based drugs. One of the methods for screening process is *in silico* screening [3].

The purpose of *in silico* screening is to find the value, rank, or filter a data structure cell using one or more computational procedures. In silico screening is used to determine the compounds to be filtered. In silico screening

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is used to determine the compounds to be filtered. In silico screening is very helpful in the synthesis process so that it saves time, energy, and costs required compared to conventional methods [5].

In this work, *in silico* screening was carried out to determine the chemical compounds contained in brotowali (*Tinospora crispa* L.) which have the potential to be antidiabetic on interactions as α-glucosidase inhibitors using the PyRx program.

METHODS

Material

The 3D structure of α-glucosidase was downloaded from the Protein Data in .pdb format. The 3D ligand structure used a chemical compound found in Brotowali (*Tinospora crispa* L.) downloaded from KNApSAcK and Zinc.

Device

The device used Lenovo G400s laptop with an Intel(R) Core(TM) i3-3110M CPU @2.40GHz 2.40 GHz processor, 4.00 GB RAM, Windows 10 Pro. The software used Protein Data Bank (PDB), KnapSack Family, Zinc, PyRx, Vega ZZ, Chimera, PyMOL, and LigPlot.

Procedure

Preparation of α-glucosidase molecular structure. The enzyme model as a receptor was prepared by downloading the α-glucosidase enzyme model from the Protein Data Bank (PDB) site with the PDB ID code of 1LWJ. Enzymes were downloaded in the (.pdb) format. Furthermore, the enzymes were optimized by separating non-standard residues and adding hydrogen atoms using the Chimera program.

Preparation of chemical compound models. Chemical compound models as test ligands were prepared by downloading the brotowali (*Tinospora crispa* L.) chemical compound model from the sites *http://kanaya.naist.jp/KNApSAcK* and *http://zinc.docking.org* and obtained 35 chemical compounds.

Optimization of the test ligand. The test ligand from Brotowali (*Tinospora crispa* L.) which had been downloaded then minimized and converted to .pdbqt format using Vegazz software.

Molecular docking. The optimized 3D structure of the test ligand of brotowali (*Tinospora crispa* L.) was docked against the α-glucosidase receptor using PyRx program (free software). The docking result parameters were based on the value of free energy (ΔG), and the interactions resulting from the docking of the the respective ligand molecules to the amino acid residues of the receptors. The lower ΔG indicated the higher compound's affinity for the receptor.

Visualization. The interaction between the receptors and the test ligands was visualized using Pymol software. Visualization was carried out by identifying the resulting amino acid residues and the similarity of the amino acid residues between the test ligand and acarbose as a comparison.

RESULT AND DISCUSSION

Molecular dockingis an *in silico* method used to analyze the interaction between receptors and ligands. The test ligands used were 35 chemical compounds from the Brotowali(*Tinospora crispa* L.) downloaded on the *KNApSAcK Family* database and Zinc database in .sdf and .mol formats. The three-dimensional structure of the ligands was then optimized using the VegaZZ program for charge and energy minimization to obtain the most stable energy molecular conformation. Optimized ligands were saved in .pdbqt format. In addition, the target receptors, α-glucosidase enzyme were downloaded from the PDB ID site with PDB ID of 1LWJwith X-ray diffraction with a specification of 2.5 Å. This macromolecule was bound to a ligand, namely acarbose. This GDP code was obtained from the research findings of Yuliana et al, 2013[6] and Najib et al, 2019 [5].

Macromolecular structures downloaded from the Protein Data Bank (PDB) were generally protein structures bound by ligands, solvents, and other non-standard residues. Then, this structure is separated from the non-standard

residue. The separation process was carried out by UCSF Chimera software. The UCSF Chimera software cut non-standard residues by not changing the arrangement of other atoms.

Molecular docking

Molecular docking was performed using the PyRx program for in silico screening. PyRx is a time-efficient software for performing in silico screening with high accuracy and prediction of bond modes. Before molecular docking, the receptor grid box was determined in advance. The grid box is the place where the ligands might interact with the residue on the enzyme target and is represented as a cube.

Each docking process began with validating the docking method using the redocking method to determine the closeness or similarity of the results between the crystallographic ligands and the redocking ligands. Thus, the docking method (the software used) was feasible or not to be used in the next docking process. Method validation was done by Calculation the RMSD (Root Mean Square Deviation) value of the target receptor and its original ligand [4].

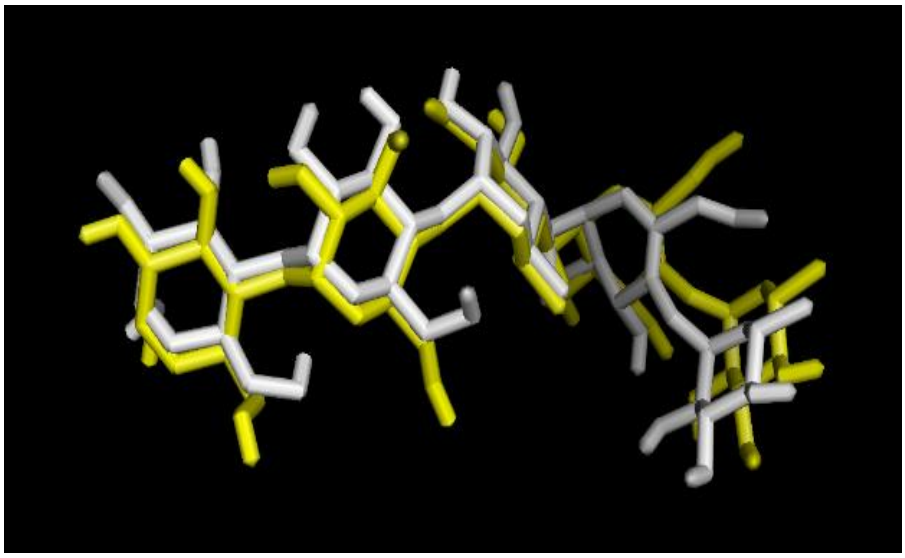

FIGURE 1. Overlay of the ligand position of the rootbose redocking result with the crystallographic ligand (Yellow = Crystallographic result; White = Redcking result)

Based on the redocking results, the RMSD value was 0.901Åwhich showed the similarity between the docking ligand and the crystallographic ligand. Therefore, the method and instrument used could be continued. The result of validation is acceptable if the RSMD value is <2 Å [7–9], . The smaller the RSMD value, the more similar the position of the docking ligands was to crystallographic ligands.

The results of ligand molecular docking with the*α*-glucosidase enzyme

The results of molecular docking were the value of bond-free energy (ΔG) and interactions that occurred between the ligand and the target protein (receptor). This interaction involves several amino acids and the types of bonds, both hydrophobic and hydrogen bonds (Pujiastuti,2017).Data from the docking results of 35 test ligands from brotowali (*Tinospora crispa* L.) with α-glucosidase receptors, obtained ΔGvalues ranging from -5.2 to -11.6 kcal/mol indicating that all compounds have an inhibitory affinity for the α-glucosidase enzyme. Where ΔG is a parameter indicating the affinity and stability of the interaction between ligand and receptor. The value of ΔG <0 indicates the interaction takes place spontaneously, and ΔG> 0 indicates the interaction cannot occur spontaneously [10,11]. Based on the results of analysis and visualization with pymol software (Figure 2), 4 test ligands had a lower ΔG value than the rootbose comparison presented in Table 1.

TABLE 1. Docking results of chemical compounds from brotowali (*Tinospora crispa* L.) with α-glucosidase receptors.

Ligand	ΔG (kcal/mol)	Contact of amino acid residues	
		Hydrogen Bonds (Bond DistanceÅ)	Hydrophobic Interactions
Acarbose	-9.8	Arg184 (3.25) ; Asp278 (3.26) ; His277 (2.99) ; His94 (3.11) ; His190 (2.70)	Thr327 ; His52 ; Tyr54 ; Ala187 ; Glu216 ; Asp278 ; Asp186 ; Phe150 ; Trp131 ; His277 ; Trp218 ; His94 ; Ala219 ; His190
N-acetylanonaine	-11.6	His190 (3.13) ; Trp131 (3.31)	Lys189 ; Ala187 ; Trp 218 ; Trp 131 ; Glu130 ; Glu216 ; His190 ; Phe150 ; Tyr322
Stigmasterol	-10.7	Ser154 (2.95) ; Asp55 (3.31)	Trp218 ; Trp131 ; Asp278 ; Phe150 ; Asp55 ; His52 ; Tyr 54 ; His94
N-Formylanonaine	-10.6	His190 (3.18) ; Trp131 (3.11)	Lys189 ; His190 ; Trp218 ; Glu130 ; Glu216 ; Trp131 ; Ala187 ; Phe150
Berberine	-10.3	His190 (3.00)	Tyr54 ; His52 ; Asp278 ; Ala187 ; Asp186 ; Phe150 ; Trp131 ; Glu216 ; Lys189 ; Trp218 ; His190 ; Glu130

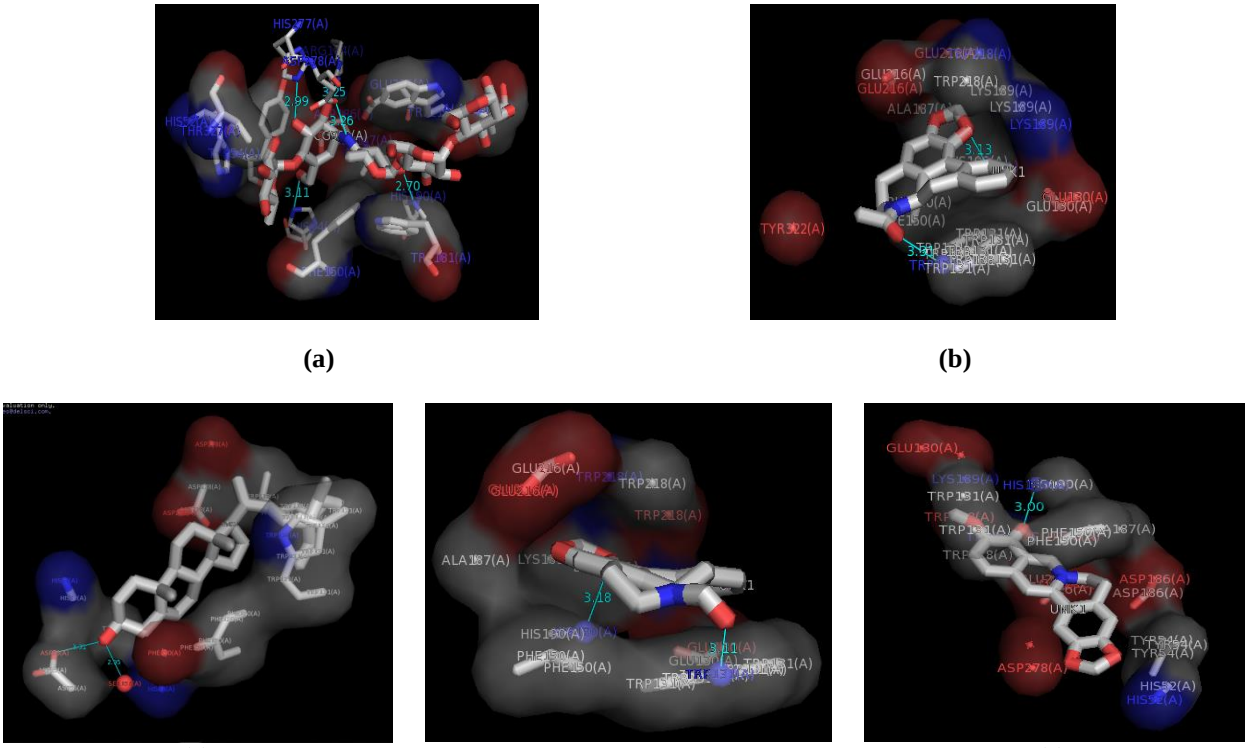

FIGURE 2. Interaction of the amino acid α-glucosidase with acarbose (a), N-acetylanonaine (b), Stigmasterol (c), N-Formylanonaine (d), and Berberine (e)

The docking results showed that the rootbose ligand as a comparison had a ΔG value of -9.8 kcal/mol with interactions to form hydrogen bonds with the amino acid residue α-glucosidase, namelyArg184; Asp278; His277; His94; His190. Furthermore, 4 ligands that had lower bond-gree energy (ΔG), namely N-acetylanonaine (-11.6 kcal/mol) with α-glucosidase amino acid residue interactions, namely His19 and Trp131, Stigmasterol (-10.7 kcal/mol) with residual interactions the amino acidα-glucosidase, namely Ser154; andAsp55, N-Formylanonaine (-10.6 kcal/mol)with the interaction of amino acid α-glucosidase residues, namely His190; andTrp131, while Berberine (-10.3 kcal/mol)with the interaction of the amino acid α-glucosidase residue, namely His19.

These data indicate that the four test ligands from the brotowali (*Tinospora crispa* L.) have a better affinity for the α-glucosidase enzyme compared to rootbose. Therefore, it is potential to be develop as a candidate for antidiabetic drugs by inhibiting the α-glucosidase enzyme mechanism.

CONCLUSIONS

Based on the results of in silico screening of the chemical compound of brotowali (*Tinospora crispa L.)* on the α-glucosidase enzyme, the following conclusions were drawn: (1)The chemical compound from brotowali (*Tinospora crispa* L.) has the potential as an α-glucosidase inhibitor. (2) There are 4 chemical compounds from brotowali (*Tinospora crispa* L.) better than acarbose which have the potential to be developed as α-glucosidase inhibitors, namely N-acetylanonaine -11.6 kcal/mol, Stigmasterol -10.7kcal/mol, N-Formylanonaine -10.6 kcal/mol,and Berberine -10.3 kcal/mol.

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