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Molecular Docking Study of Takokak Plants (Solanum torvum) to α-glucosidase as Antidiabetic Type-2

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ABSTRACT

Diabetes mellitus is a serious chronic disease that occurs when the pancreas does not produce enough insulin (a hormone that regulates blood sugar or glucose), or when the body cannot effectively use the insulin it produces. The fruit of the takokak plant (*Solanum torvum*) is widely used in traditional medicine systems to treat diabetes mellitus. This study aimed to analyze the interaction of the active compound in takokak plant against *α-glukosidase* as a type-2 antidiabetic. This research method uses molecular docking analysis run using PyRx Software and visualized with Biovia Discovery Studio. Molecular docking analysis was aimed at looking at the binding energy between -glucosidase (PDB ID: 3W37) and the active compound of takokak plant consisting of Methyl caffeate (CID 689075), Phytol (CID 5280435), Neophytadiene (CID 985) and Hexadecanoic acid (CID 10446). The data obtained in the form of Root Mean Square Diviation (RMSD), binding affinity and amino acid residues. The results of this study indicate that there are four active compounds that have antidiabetic activity in takokak plants. The results of molecular docking compound analysis showed that methyl caffeate was the best compound compared to the control in inhibiting *α-glukosidase* with a binding affinity value of -6.8 (kcal/mol) so that the takokak plant could be recommended as a type-2 antidiabetic drug.

Keywords:

Antidiabetic type-2, molecular docking, takokak, α-glucosidase

INTRODUCTION

Diabetes mellitus is a serious chronic illness that occurs because of the pancreas. Doesn't produce enough insulin (hormones that control blood sugar or glucose), Or when the body cannot effectively use the insulin it produces. Diabetes mellitus is an important public health problem, being wrong. One in four non-communicable diseases has a priority that becomes a follow-up target world leaders. The number of cases and prevalence of diabetes continues to rise during the lifetime. Recent decades [1].

Tipe-2 diabetes mellitus It's a metabolic disease that was flagged as a sugar rise. Blood from a degenerative secretion of insulin by the beta cells of the pancreas and or disorders. On insulin function (insulin resistance). It's a 2008 primary health study. Showing the incidence of diabetes mellitus in Indonesia reaching 57%, while world events, type 2 diabetes mellitus is 95% [2].

Takokak (*Solanum torvum swartz*) is often a traditional plant used as vegetables, fruits, decorative plants and were used for various

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purposes drug use [3]. A takokak belongs in one of the plants Indonesian-based drug which part of the fruit is often consumed by society. According to this part of the plan, according to the plant, according to the plant young and green after old orange. The first takokak got it harvested after a plant is about 3-4 months old from planting time, fruit is picked is usually an almost old fruit [4].

Some results have suggested that a takokak plant is a plant used in treating infections that have pretty good antibacterial activity. Plants takokak is from the islands of Antilles, and a spread of growth to tropical countries including Indonesia, it grows in the Sumatran region, Java, and in the lower plain to 1 - 1,600 m above sea level, where it is not too run off and quite firm moderate sun [5].

The use of *S.torvum* as a medicine is linked to its secondary metabolic properties or its bioactive compound, which differs somewhat from one organ to another. *S. torvum* leaves have about 32 types of compounds with primary components of phenolic compound, turpentine, palmitate acid, palmitic acid, acid lonoleates, linolenyl alcohol, estem linolenic acid and stearic acid, while fruit hikes are found with alkaloids, flavonoids and certain fatty acids such as palmitate and oleic acid, whereas seeds 31 types of phytogenic compounds [6]. In ethnobotanical *S. torvum* is used for the treatment of fever, wounds, tooth decay, problems of reproductive and hypertension of the arteries of asthma, diabetes mellitus, intestinal and eye disorders, cataracts, some scribes have shown that solanum torvum has analgesic and anti-inflammatory activities [7].

Research conducted by Silalahi (2019) diabetes millitus type 2 has more sufferers especially in advanced humans. Insulin is a hormone that can function to regulate the glucose metabolism in the blood by converting excess glucose into a glycogen stored in the liver. The *Solanum torvum* fruit is widely used in traditional medicine systems to treat diabetes mellitus. The dried fruits of the *S. torvum* are extracted by 50% of methanol, containing *methyl caffeate* [6].

Many pharmacological studies indicate that the plant has antiplatelets, analgesic, anti-inflammatory, and anti-microbial activity, and many more related to the constituency of phytochemistry. The river *S. torvu*m leaf antibacterial potential for some pathogenic bacteria in humans and plants has been studied. However, the study mainly uses water, chloroform and methanol as extraction solvents. Furthermore, the constituency of plant phytochemistry has been investigated extensively as source of a drug agent. Given the increasingly difficult problem of microbial resistance against most antibiotics, medicinal plants are now being considered as alternatives to disease treatment [8].

Virtual research at this time is still scarce. *Virtual research* conducted is intended to reduce the potential for clinical trials as they do in most studies. Furthermore, research is done in silico which means research is done with using existing software to determine the interaction between drugs and pathogens in the body. *Molecular docking* or molecular moorings are used because of its ability to predict conformation in target receptors with high levels of accuracy. The

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purpose of docking is to predict links between small molecules (ligan) and target receptors with the best affinity [9].

Based on the above problems, the purpose of this study is to analyze the effects of active compounds on α-glucosidase as antidiabetes in silico.

METHOD

The study uses *Molecular docking* analysis. *Molecular Docking* analysis is intended to see the bond energy between *α-glucosidase* and active compound takokak. The parameters used are the value of the drug criteria based on the *Root Mean Square Diviation* (RMDS) and *binding affinity*. In the *Molecular docking* stage of analysis aims to predict the active compound interactions of *α-glucosidase* antidiabetes of type 2.

a) Ligan Preparation

The research used ligan's recovered from the PubChem WebServer protein analysis of the target. Based on the search for ligan on the web found 4 active compounds used in research (Table. 1)

Table 1. Preparing ligan

No	Senyawa Aktif Tanaman Takokak
1	Methyl caffeate (CID 689075), Neophytadiene (CID 985), Hexadecanoic acid (CID 10446)
	Total senyawa uji : 4 senyawa dan 1 native ligand (2-acetamido-2- deoxy-beta-D-glucopyranose)

b) Preparation Protein Reseptor

The molecular structure of the receptors used by *α-glukosidae* PDB ID: 3W37 can be downloaded using the RCSB PDB server Web (https://www.rcsb.org). Preparations are made by removing unneeded ligan, chain, and water molecules then stored in PDB format.

c) Molecular Docking Stage

Ligation-target docking computations are implemented to analyze the complex structure of *α-glukosidase* as target, *Molecular docking* analysis is run using PyRx and Biovia Discovery Studio. The docking analysis shows links and links to ligan's receptors. The first thing to do is to enter the target protein (receptors) and ligan who have been in the preparation of the application. Next, after target proteins and ligan's input then proceed with box grid Settings. Then comes *Molecular docking*. Molecular moorings are then stored in PDBQT format to continue at the next stage.

d) Validation Stage and Docking Result Visualization

Validation and visualization of *Molecular docking* interactions using the Discovery studio virtual software. To see the interactions generated by *Molecular docking*, further visualization, 2D and 3D were used for the Discovery studio virtual software. Visualize results can show the interaction of amino acids in the form of 2 dimensions and 3 dimensions. Further on the interactions were analyzed the links forming between the receptors and ligan.

The results of this study take secondary data from databases that are then systematically collated into tables and pictures by reading data based on research based on RMSD values, bindings and amino acid interactions.

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RESULT AND DISCUSSION

Diabetes mellitus is a disease characterized by hyperglycemia and carbohydrate, fat, and protein metabolism that are associated with absolute or relative deprivation of work and or the secretion of insulin. Symptoms complained about with diabetes mellitus of Polidipsia, Polyuria, Polifagia, weight loss, tinglity. The high prevalence of diabetes melnitus type 2 is caused by an unchanging risk factor such as gender, age, and genetic factors as the second changeable risk habits such as smoking habits, work, physical activities, smoking habits, alcohol consumption, body mass index, waist and age [10].

Some bacteria that cause diabetes are such bacteria as *Staphylococcus* or *Pneumoniae Klebsiella*. One of the methods of treating mellitus diabetes that is developing is the inhibiting activity of *α-glucosidase* enzymes with a compound compounding *α-glucosidase* inhibitors. The *α-glucosidase* inhibitors are described as the most effective in reducing post-prandial hyperglycemia (PPHG) of all the available anti-diabetic drugs used in the management of type 2 diabetes mellitus [11].

α-glucosidase inhibitor is a compound capable of intubation a complex carbohydrate metabolism into glucose in the small intestine. The activity of a complex glucose kosidase will reduce the number of glucose entering from the intestines to the blood. With such activity, it has been able to reduce the increase in blood glucose levels in diabetes patients. Compounds of microscopic inhibitors *α-glucosidase* and endofit microbes that live in symbiosis with them [12].

Some studies have proved that takokak plants as a medicine are linked to their secondary metabolic properties or their bioactive compounds, which differ relatively from one organ to another. The leaves of the *S. torvum* have some 32 types of compounds with the main components of phenolic, desert, palmitate acid, palmitate acid, linolenyl alcohol, estem linenic acid and stearic acid while at fruit extracts are found alkaloids, flavonoids and certain fatty acids such as palmitate and oleic acid, while the seeds have 31 types of phytogenic compounds [6]. Of some of these chemicals, it is said that birth-chemical properties found in takoak fruits can have a pharmacological effect, such as spicy, cool, and toxic [13].

Moleculer docking is a way of looking ata compound that produces biological effects when it bonded with a glucosidase receptor. *Moleculer docking* is done by interning the most potential compounds derived from target protein analysis. *Moleculer docking* is engaged to learn the interactions generated between 4 active compounds in takokak plants and *α-glucosidase* receptors. The *moleculer docking* results in interactions demonstrated by the bond of amino acid residue. Image results from interactions of active compounds with shared *α-glucosidase* receptors can be seen in the following pictures:

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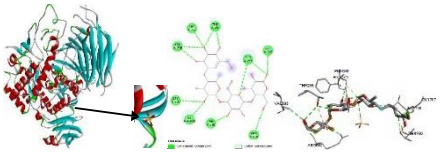
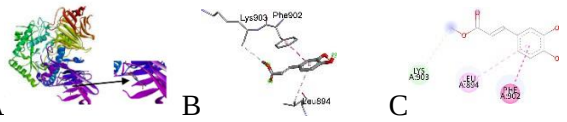


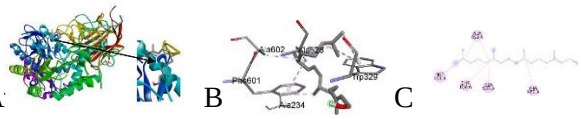
A B C

Image 1. (A) simulated *moleculer docking* protein *α-glucosidase* (PDB ID : 3W37) with *2-acetamido-2-deoxy-beta-D-glucopyranose* (Native ligan a- glukosidase); (a) Kompleks protein-ligan; (b) 3D structure interaction; and (c) 2D structural interaction



A B C

Image 2. (A) simulated *moleculer docking* protein *α-glucosidase* (PDB ID : 3W37) with *Methyl caffeate*; (a) Kompleks protein-ligan; (b) 3D structure interaction; and (c) 2D structural interaction.



A B C

Image 3. (A) simulated *molecular docking* protein *α-glukosidase* (PDB ID: 3W37) dengan *Phytol*; (a) Kompleks protein-ligan; (b) 3D structure interaction; and (c) 2D structural interaction.

A B C

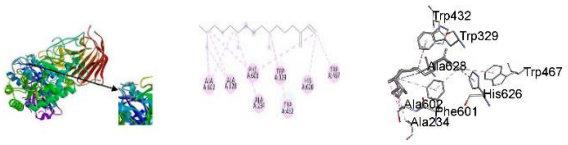
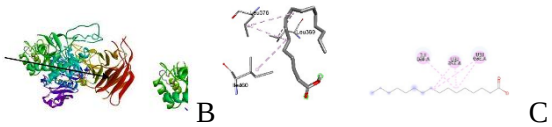


Image 4. (A) simulated *moleculer docking* protein *α-glucosidase* (PDB ID : 3W37) with *Neophytadiene*; (a) Kompleks protein-ligan; (b) 3D structure interaction; and (c) 2D structural interaction.



A B C

Image 5. (A) simulated *moleculer docking* protein *α-glucosidase* (PDB ID : 3W37) with *Hexadecanoid acid*; (a) Kompleks protein-ligan; (b) 3D structure interaction; and (c) 2D structural interaction.

Molecular docking is a high-value bonding energy obtained between active compounds and demonstrated *α-glukosidase* receptors. In addition, *molecular docking* produces interactions of amino acid residue with various types of bonds. The result of an interaction of amino acid residue between an active compound and a color-glucosidase target protein can be seen at Table 2.

Tabel 2. The results of amino acid residue interaction with proteins

No	Compound name	Value Binding affinity	Interaction type
1	Control/*2-acetamido-2-deoxy-beta-D-glucopyranose*	-6,2	Bond Hidrogen VAL 303, THR 299, ARG 670, PHE 680, ARG 676, ASN 758, GLY 757, THR 790
2	*Methyl caffeate*	-6,8	Bond Hidrogen LYS 903 Bond Hirofobik LEU 894, PHE 902
3	*Phytol*	-5.7	Bond Hidrofobik ALA 234, ALA 602, PHE 601, TRP 329, ALA 628
4	*Neophytadiene*	-5,5	Bond Hidrofobik ALA 602, ALA 628,

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No	Compound name	Value Binding affinity	Interaction type
			PHE 601, ALA 234, TRP 329, TRP 432, HIS 626, TRP 467
5	Haxadecanoic acid	-4,2	Bond Hidrofobik LEU 369, LEU 376, ILE 460

There are four amino acid resizes that are bound between *α-glukosidase* target proteins and *Methyl caffeate*, a bond composed of hydrogen LYS 903. The hydrophobic bond LEU 894, PHE 902. Value binding affinity for a large -6.8 kkal/ mole. The *Pythol* is tied with 5 amino acid residue of the Hydrofobic bond with amino acid, ALA 234, ALA 602, PHE 601, TRP 329, ALA 628. Value binding affinity earned at -5.7 kkal/ mole. *Neophyhyene* is bound with 8 amino acid residue of 602, ALA 628, PHE 601, ALA 234, TRP 329, TRP 432, HIS 626, TRP 467. Value binding affinity earned by -5.5 kkal/ mole. *Hexadecanoic acid* is tied with 3 amino acid residue of LEU 369, LEU 376, ILE 460. Value binding affinity earned by -4.2 kkal/ mol.

CONCLUSION

Based on *molecular docking*, the compound *methyl caffeate* is the best active compound for *α-glukosidase* receptors. This is because they have greater accouplets than other substances and control compounds.

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