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Virtual Assessment of *Imperata Cylindrica* Root's Bioactive Compounds as a Potential Inhibitor for Alpha-Glucosidase: the Study of Tengger Tribe's Medicinal Plant

Fatchur Rohman[1]*, Wira Eka Putra[1,2], Sustiprijatno[3], Diana Widiastuti[4]

[1]*Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, East Java, 65145, Indonesia*
[2]*Department of Biotechnology, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, East Java, 65145,Indonesia*
[3]*Indonesian Center for Agricultural Biotechnology and Genetic Resources Research and Development, West Java, 16111, Indonesia*
[4]*Department of Chemistry, Faculty of Mathematics and Natural Science, Universitas Pakuan, West Java, 16129, Indonesia*

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ABSTRACT

One common clinical sign of type 2 diabetes mellitus is a high level of glucose in the blood. This condition leads to a worsen outcome for the patient and is often followed by a complication. Thus, the strategy to prevent this adverse effect is to inhibit alpha-glucosidase activity, which was known as enzymes that convert carbohydrates into glucose. Indonesia, as a mega biodiversity country, has multiple type of medicinal plants that are used to ameliorate diseases. Tengger tribe, one of ethnic group of Javanese which live in eastern Java, has a local wisdom related to the medicinal plants. The present study aimed to virtually assess one of Tengger Tribe medicinal plants called *Imperata cylindrica* as an anti-diabetic agent. Virtual screening was performed to evaluate the bioactive compounds. Several indicators were measured, such as the minimum baseline for drug-like compounds candidate, binding affinity scores, chemicals interaction pattern, and residual amino acid between the ligand and the target protein. According to our findings, numerous bioactive compounds such as 5-methoxyflavone, 6-hydroxy-5-methoxyflavone, 7-hydroxy-4-methoxy-5-methylcoumarin, and Siderin have potency as drug-like compound and have higher binding affinity to the alpha glucosidase as target protein compared with Miglitol as a control drug for alpha-glucosidase. From this computational prediction, the future in vitro and in vivo study to evaluate 5-methoxyflavone, 6-hydroxy-5-methoxyflavone, 7-hydroxy-4-methoxy-5-methylcoumarin, and Siderin anti-diabetic effect against alpha-glucosidase is necessary.

***Keywords*:** Alpha-glucosidase, Hyperglycemia, Medicinal plant, Tengger Tribe, Type 2 Diabetes Mellitus.

Introduction

Type 2 diabetes mellitus (T2DM) is a severe chronic and systemic disease.[1,2] Recently, T2DM has become a severe issue worldwide due to its annual increase and prevalence.[3,4] The disease has been associated with cruddy lifestyles; for example, physical inactivity, sedentary lifestyle, cigarette smoking, generous consumption of alcohol, and uncontrolled food intake are common causes of insulin resistance.[5-7] Approximately 55% of T2DM patients were found to be obesed.[8] Further, recent rises in the T2DM rate were caused by an environmental toxin.[9] Importantly, insulin resistance has defective effects on glucose intake and the metabolism of the cells. This undesirable condition leads to hyperglycemia, which was indicated by the elevation of glucose level in the blood.[10] T2DM screening and diagnosis are easily accessible.[11] Besides, several efforts have been proposed to alleviate the clinical condition of T2DM, including routine body exercise, synthetic insulin injection, or alpha-glucosidase inhibitor administration.[12,13] Despite these, several reports showed positive results on T2DM treatment by using those modalities. However, in this study, we attempted to find new alpha-glucosidase inhibitors from natural materials since Indonesia is considered a mega-biodiversity country. Furthermore, this study focused on alpha-glucosidase, which has a pivotal role in the destructive metabolism of carbohydrates as a complex biomolecule into glucose as the simple ones.[13] The alpha-glucosidase enzyme catalyzes the hydrolysis of glucose biomolecules in a brush boundary of jejunum enterocytes, resulting in monosaccharides consumed in the jejunum.[14] By inhibiting this enzyme's biological activity, it decreases the glucose level in the blood, and it might reduce the other adverse effects in the T2DM condition. Interestingly, inhibitors reversibly enhance the removal of sugar from the gut by inhibiting various alpha-glucosidase enzymes. Further, in a recent study investigating healthy subjects, the therapeutic impacts of inhibitors were focused solely on the delayed digestion of complex sugar and colonic starch fermentation.[15,16]

Natural phenolic compounds have gained popularity in recent years since many of them can be found in plants. Further, the consumption of vegetables and beverages high in such compounds can, among other things, help prevent several diseases due to their antioxidant properties.[17] As in our previous study that identified Tengger Tribe medicinal plants, we revealed that *I. cylindrica* root had been used for therapeutic purposes in several types of diseases: toothache, diarrhea, heat suppressor, and reducing high blood pressure.[18] The *I. cylindrica* is a group of grass that is widely found in many areas, especially in Southeast Asia. Interestingly, another study conducted by Liu *et al* (2013) demonstrated that *I. cylindrica* root contains several critical bioactive compounds such as 5-methoxyflavone, 6-hydroxy-5-methoxyflavone, 7-hydroxy-4-methoxy-5-methylcoumarin, and Siderin.[19] It is well recognized that dietary flavonoids play a significant role in the prevention of degenerative diseases. Furthermore, higher flavonoid intakes are related to a lower incidence of type 2 DM, according to epidemiological studies. In addition to their preventive role, flavonoids also treat diabetes effectively in several

*Corresponding author. E mail: fatchur.rohman.fmipa@um.ac.id
Tel: 0341-552180

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experiments.[14] Therefore, in this present study, we aimed to evaluate and screen the anti-diabetic potency of those compounds against the alpha-glucosidase as the target protein through in virtual screening.

Bioinformatics is a transdisciplinary working field that includes several research areas: biology, medicines, chemistry, mathematics, and computer science. One of the mushrooming discussions in this issue is the creation of drugs using computers and intelligent algorithms called in silico methods. Further, virtual screening, on the other hand, is a computer technique for researching small molecule libraries in the discovery of medicines to recognize certain structures that most frequently bind to a drug target, usually a protein receptor or enzyme.[20] The key components of recent pharmaceutical research are goal and lead discovery. The aim is to define and validate effective drug targets for treatment interventions and identify new chemical molecules for therapeutic intervention.[21]

Materials and Methods

The *I. cylindrica* root's bioactive compounds, including 5-methoxyflavone, 6-hydroxy-5-methoxyflavone, 7-hydroxy-4-methoxy-5-methylcoumarin, and Siderin were used as ligands for screening as demonstrated by Liu *et al*. (2013).[19] Miglitol, alpha-glucosidase inhibitor, was used as a positive control to compare its binding affinity to the bioactive compounds (see Table 1). The 2D structure of ligands and control drugs were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). PubChem is one of the most extensive public archives and database for information on chemical substances and their biological function and activity.[22]

On the other hand, the 3D protein structure of alpha-glucosidase was made online via SWISS-MODEL (https://swissmodel.expasy.org/). Ligands optimization was done prior to molecular docking procedures. The Lipinski rule of five was used to determine and evaluate the ligands used in this study. Completing these five indicators is crucial to deciding which compounds can proceed for the next steps and consider a drug-like compound.[23] Finally, the final steps were molecular docking, visualization, and data analyses.[24-26]

Results and Discussion

An increased blood glucose level characterizes type 2 mellitus diabetes, leading to severe complications such as nephropathy, neuropathy, and retinopathy.[27-28] The digestion of dietary carbohydrates is impaired by therapeutic approaches to postprandial hyperglycemia treatment in type 2 diabetes mellitus. Pancreatic alpha-amylase is a crucial enzyme that splits dietary carbohydrates like starch in the digestive system into simple monosaccharides. These are further degraded to glucose by α-glucosidases that enter the bloodstream after absorption.[29,30] In the T2DM case, the high glucose level in the blood worsens the patients' condition. This undesired condition is often followed by other complications such as cardiovascular disease, bone and joint problems, diabetic nephropathy, and diabetic retinopathy.[31,32] Inhibiting alpha-glucosidase activity in the T2DM patients is crucial to minimize the glucose level in the blood, since the T2DM patient clinically underwent insulin resistance.

Computational prediction found that the bioactive compounds from the root of *I. cylindrica* have eminent potency as an inhibitory agent of alpha-glucosidase. In the figure 1, we found that each ligand interacts and binds to the alpha-glucosidase. This interaction might change the alpha-glucosidase conformation, leading it to fail to convert the carbohydrate into glucose. Interestingly, the prediction also showed the binding affinity of bioactive compounds i.e., 5-methoxyflavone, 6-hydroxy-5-methoxyflavone, 7-hydroxy-4-methoxy-5-methylcoumarin, and Siderin were greater than Miglitol as control drug for alpha-glucosidase inhibitor (Table 1). The smaller the ligand's binding affinity to the target protein, the greater the ligand can have stable bonds to the target protein.[24,25] In this report, we also showed the properties of 5-methoxyflavone as potential inhibitory drug against the alpha-glucosidase, which include physicochemical properties, drug likeness, chemical structures, and also the target class of protein (see Figure 2).

Additionally, we showed the chemical interaction between the ligands and the target protein from this computational prediction. In Table 2, we summarized the chemical interaction from all compounds that bind to alpha-glucosidase.

To a greater extent, there is a similar pattern of chemical interaction that builds Miglitol compared to the *I. cylindrica* root's bioactive compounds. This study demonstrated that all ligands interaction to target protein have van der Waals and conventional hydrogen bonds.

Relatively weak interactions are hydrogen bonds, which are nevertheless essential for biological macromolecules, including DNA and proteins. Hydrogen bonding is a hydrogen atom interaction found between a pair of other atoms with a high electron affinity; such a bond is weaker than an ionic bond or covalent bond but more robust than van der Waals' forces. In different molecules or parts of the same molecule, hydrogen bonds may exist between atoms. These interactions have many of the features of water that make it such a particular solvent. The hydrogen atom is partially divided into two comparatively electronegative atoms, such as nitrogen and oxygen, within a hydrogen bond.

Table 1: Physicochemical properties and binding affinity scores of *I. cylindrica* natural compounds

Compounds	Molecular Mass (Dalton)	LogP	H-Bond Donors	H-Bond Acceptors	Molar Refractivity	Binding Affinity (kcal/mol)
5-methoxyflavone CID: **94525**	252	2.58	0	3	63.43	-7.3
6-hydroxy-5-methoxyflavone CID: 14349485	268	2.21	1	4	65.63	-7.1
7-hydroxy-4-methoxy-5-methylcoumarin CID: 5318268	206	1.10	1	4	47.40	-7.0
Siderin CID: 185740	220	1.81	0	4	52.68	-6.6

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The hydrogen bonds donor consists of both the hydrogen-connected atom and hydrogen itself; the hydrogen-bonding atom is not nearest to the hydrogen atom. The atom is the hydrogen-bundling atom. Hydrogen connections are electrostatic interactions.[33]

It is understood that plant metabolism is divided into primary and secondary metabolic processes. The primary metabolism originates from substances that are common to living things and important to cell maintenance, such as lipids, proteins, carbohydrates, and nucleic acids. Substances derived from many biosynthetic pathways, on the other hand, which are confined to particular groups of species, are the products of secondary metabolism. In one of the largest and widely distributed classes of secondary metabolites in plants, phenolic compounds were constituted.[17] In plants, phenolic compounds are a primary metabolite class and are split into phenolic acids and polyphenols. These compounds, connected to one or more phenolic groups, are present in combination with mono- and polysaccharides or can occur as derivatives, such as esters or methyl esters. Phenolic acids, flavonoids, and tannins are known as the major dietary phenolic compounds among several phenolic compounds. A strong and positive link between the phenolic compound's content and the antioxidant ability of fruits and vegetables has been shown in several studies. This antioxidant function, which is present in plants, plays an essential role in minimizing lipid oxidation in plant and animal tissues since it maintains the quality of food when introduced into the human diet and decreases the risk of contracting certain diseases. Studies have shown that a diet rich in fruits and vegetables slows the aging process and reduces the risk of chronic disease-related inflammation and oxidative stress.[34] However, the phenolic compounds' antioxidant activity depends on a large part upon the chemical structure.[17] Further, several compounds from the root of *I. cylindrica*, including 5-methoxyflavone, 6-hydroxy-5-methoxyflavone, 7-hydroxy-4-methoxy-5-methylcoumarin, and Siderin are grouped into phenolic compounds.[19] A study conducted by Huang *et al*. (2009) elaborated the medicinal function of the phenolic compounds in the biological system, including antioxidant, anti-carcinogenic, anti-inflammatory, inducing proliferation, and blocking signaling pathways.[35]

Plant-based enzyme inhibitor can be more recommended because of safety issue compared to synthetic. Several experimental works have been done to reveal the potency of numerous phenolic compounds against hyperglycemia-induced chronic diseases. For instance, multiple phenolic compounds from raspberry have been shown to have an inhibitory effect against alpha-amylase and alpha-glucosidase.[36] Other phenolic compounds, namely (-)-3-*O*-galloylepicatechin and (-)-3-*O*-galloylcatechin isolated from Bergenia ciliate, successfully demonstrated a high inhibition rate on starch digesting enzymes.

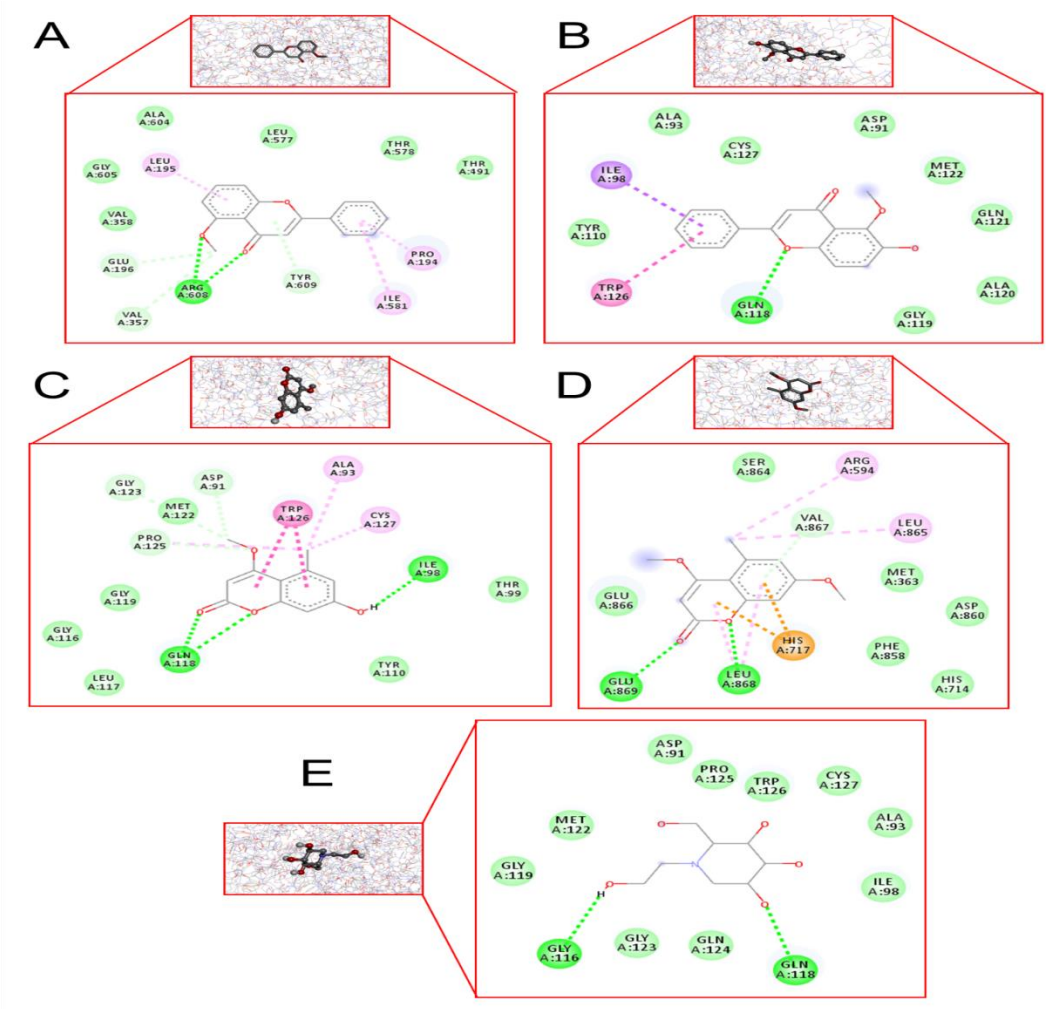

Figure 1: Schematic pattern of ligands and target protein interaction. The ligands used in this experiment from the *I. cylindrica* natural compounds, i.e. **A**. 5-methoxyflavone, **B**. 6-hydroxy-5-methoxyflavone, **C**. 7-hydroxy-4-methoxy-5-methylcoumarin, **D**. Siderin, and **E**. Miglitol as control.

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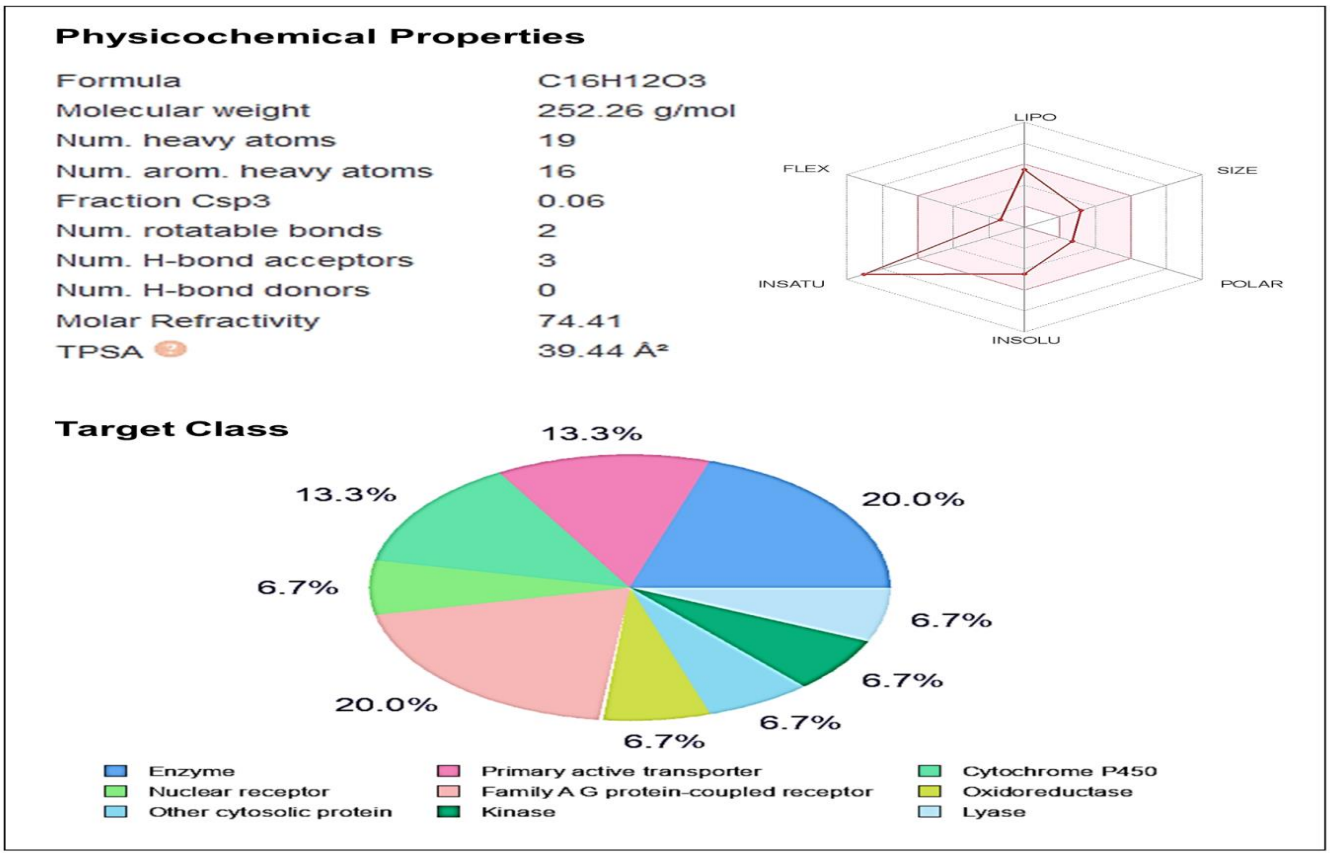

Figure 2: The properties of 5-methoxyflavone as a potential inhibitory drug candidate for alpha-glucosidase. Several properties showed including the physicochemical properties and the target class of protein.

Table 2: Chemical interaction between the *I. cylindrica* natural compounds and alpha glucosidase as target protein

Ligands	Target Protein	Chemical Interaction	Residual Protein
5-methoxyflavone CID: **94525**	Alpha Glucosidase	van der Waals Conventional Hydrogen Bond Carbon Hydrogen Bond Pi Donor Hydrogen Bond/ Pi-Alkyl	VAL A:357, GLU A:196, TYR A:609 ARG A:608 TYR A:609, VAL A:357, GLU A:196 PRO A:194, ILE A:581, LEU A:195
6-hydroxy-5-methoxyflavone CID: **14349485**	Alpha Glucosidase	van der Waals Conventional Hydrogen Bond Pi-Sigma Pi-Pi Stacked	TYR A:110, ALA A:93, CYS A:127, ASP A:91, MET A:122, GLN A:121, ALA A:120, GLY A:119 GLN A:118 ILE A:198 TRP A:126
7-hydroxy-4-methoxy-5-methylcoumarin CID: **5318268**	Alpha Glucosidase	van der Waals Conventional Hydrogen Bond Carbon Hydrogen Pi-Pi Stacked Alkyl	THR A:99, TYR A:110, LEU A:117, GLY A:116, GLY A:119, MET A:122 ILE A:98, GLN A:118 PRO A:125, GLY A:123; ASP A:91 TRP A:126 ALA A:93, CYS A:127
Siderin CID: **185740**	Alpha Glucosidase	van der Waals Conventional Hydrogen Bond Pi-Cation Pi-Donor Hydrogen Bond Pi-Alkyl/ Alkyl	GLU A:866, SER A:864, MET A:363, ASP A:860, PHE A:858, HIS A:714 LEU A:868, GLU A:869 HIS A:717 VAL A:867 ARG A:594, LEU A:865
Miglitol CID: **441314** (Control Drug)	Alpha Glucosidase	van der Waals	GLY A:119, MET A:122, ASP A:91, PRO A:125, TRP A:126, CYS A:127, ALA A:93, ILE A:98, GLN A:124, GLY A:123

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Conclusion

The present study has shown the potency of the root extract from *I. cylindrica* as drug-like compounds, especially as anti-diabetic agents. Numerous bioactive compounds such as 5-methoxyflavone, 6-hydroxy-5-methoxyflavone, 7-hydroxy-4-methoxy-5-methylcoumarin, and siderin have higher binding affinity to the alpha-glucosidase as target protein compared with miglitol as a controlled drug for alpha-glucosidase. Further research is needed from these computational predictions, especially for the *in vitro* or *in vivo* experiment to evaluate the compounds' biological effects.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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