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Evaluation on Bioactive Secondary Metabolites from Fingerroot (*Boesenbergia rotunda*) as a Potent α-Glucosidase Inhibitor: In silico Study

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ABSTRACT

Fingerroot (*Boesenbergia rotunda*) is a medicinal plant that has been reported to have anti-diabetic properties. However, the mechanism of action and the active compounds responsible for this effect are not well understood. In this study, we performed molecular docking study of isolated compound from fingerroot against N-terminal-human intestinal maltase-glucoamylase, one class of α-glucosidase. Inhibiting enzymatic activity of alpha glucosidase could potentially control sugar levels. In addition to panduratin A showing moderate inhibition activity against N-terminal-human intestinal maltase-glucoamylase.

1. Introduction

Fingerroot, also known as temu kunci, krachai or fingerwurz, is a plant that belongs to the ginger family (Zingiberaceae) [1]. It is native to India, Sri Lanka, China and Southeast Asia, where it is widely used as a culinary herb and a traditional medicine [2]. The name fingerroot comes from the shape of its rhizomes, which resemble fingers growing out of a central piece [3]. Fingerroot has various health benefits, such as anti-inflammatory, antioxidant, antibacterial, and anti-cancer properties [4], [5]. Notably, research has demonstrated that fingerroot extracts possess alpha-glucosidase inhibitory activity [6] suggesting a potential role in managing metabolic disorders such as diabetes mellitus type 2.

Diabetes mellitus type 2 is a chronic metabolic disorder characterized by high blood sugar levels due to insulin resistance or deficiency. It is a major public health concern worldwide,

with an estimated 463 million adults affected in 2019 [7]. Alpha-glucosidase inhibitors are a class of oral anti-diabetic drugs that can help manage type 2 diabetes by delaying the absorption of carbohydrates in the gut [8]. In addition to their anti-diabetic effects, α-glucosidase inhibitors have also been shown to have beneficial effects on glycemic control, insulin levels, and post-load blood glucose [9].

Alpha-glucosidase is a type of enzyme that catalyzes the hydrolysis of alpha-linked glycosidic bonds in carbohydrates, such as starch, maltose, isomaltose, and sucrose [10]. In humans, there are two intestinal alpha-glucosidases, maltase-glucoamylase (MGAM) and sucrase-isomaltase (SI), which are responsible for the final step of carbohydrate digestion in the small intestine [11]. Each of these enzymes has two catalytic domains, an N-terminal domain (NtMGAM and NtSI) and a C-terminal domain (CtMGAM and CtSI), which have different substrate specificities and affinities [12]. NtMGAM is one of the catalytic domains of MGAM, which preferentially hydrolyzes alpha-1,4-linked glucose polymers, such as starch and glycogen [13]. Inhibition of NtMGAM and other α-glucosidase domains can reduce the postprandial glucose spikes and improve glycemic control in patients with type 2 diabetes [14], [15]. Several natural and synthetic compounds have been identified as alpha-glucosidase inhibitors, such as acarbose, voglibose, salacinol, and kotalanol [16].

In silico study is a computational method that integrates biology, chemistry, and medicine to predict outcomes, propose theories, and facilitate discoveries in medicine and therapy [17]. Molecular docking studies are one of the widely used in silico methods for novel drug development, as they efficiently screen compounds by providing key information about the binding mode of a ligand to its receptor and its binding affinity. Moreover, molecular docking is a fast and computationally efficient approach, making it ideal for initial screening in drug discovery [18]. In this study, we aim to investigate the binding mode of two previously isolated compounds, pinostrobin **(A)** and panduratin A **(B) (Figure 1)**, which have been reported as antidiabetic agents from fingerrot as an anti glycating agent (Potipiranun et al., 2018). However, in this study, we will focus on the molecular docking of isolated compounds with alpha-glucosidase to provide insights into their interactions with the target receptor, offering new perspectives on ligand binding modes to alpha-glucosidase and their potential therapeutic implications. However, further studies are needed to gain a more comprehensive understanding of their dynamic behavior and binding stability.

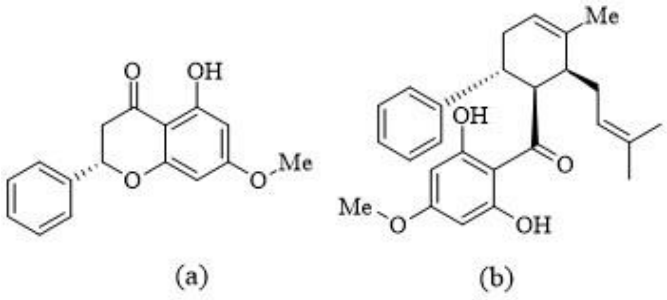

Figure1. (a) Pinostrobin; (b) Panduratin A that isolated from fingerroot

2. Materials and methods

Crystal structure of ntMGAM (3L4W) that complexed with miglitol was retrieved from rcsb.org [19], [20]. Docking preparation was performed with Chimera 1.16's Dock Prep [21]. In order to verify the docking parameter of the receptor and its native ligand, redocking was undertaken before docking with the ligand. The *sphgen* tool was employed to generate the molecular surface. The *sphere selector* tool was used to pick the spheres with a radius of 7.0 Å from the ligand, as the precise position of the enzyme is known. A grid box was generated with the range of 7.0 Å in all directions. Soft docking was carried out with Lennard-Jones 9-6 potential using GRID software. The docking process was executed with DOCK6 program [22].

The ligand of pinostrobin and panduratin A was built and optimized by Avogadro using MMFF94, and then the AM1-BCC electrostatic charge was utilized by the ANTECHAMBER program for the protein [23], [24]. The ligand was docked to the receptor using the same parameters as the redocking procedure. Docked ligand interaction was visualized using UCSF ChimeraX version 1.8 and Biovia, D.S. (2024) Discovery Studio Visualizer. San Diego.

3. Results and discussion

The result of molecular docking from DOCK6 provides score information, grid score, which consist by sum of grid van der Walls and grid electrostatic. In this study we compare pinostrobin and panduratin A as ligand experiments and miglitol as the native ligand and commercially available drug.

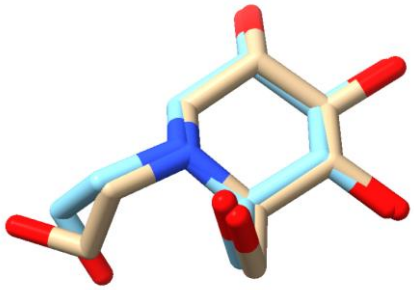

Figure 2. Redocking validation with RMSD: 0.5614Å

Prior to docking to an experiment ligand, redocking was carried out to validate docking parameter. Redocking of the native ligand (Miglitol) to the ntMGAM resulted in a Grid score of -75.872 and an RMSD of 0.5614 Å, this method is considered valid to use for further docking studies as the value of RMSD is less than 2.0 **(Figure 2)** is showing superimposing of miglitol. Miglitol as the standard in this molecular docking process, exhibited the strongest binding affinity, with van der Waals contributing value of -38.704 and electrostatic interactions of -37.167. Furthermore, it was revealed that several residues interact with miglitol by forming hydrogen bonds with Asp327, His600, Asp542, Arg526, and Asp443.

Table 1. The result of docking molecular (PDB ID: 3L4W)

Compound	Grid Score	Grid vdW	Grid Electrostatic	Type	Interaction
Miglitol	-75.872	-38.704	-37.167	Hbonds	Asp327, His600, Asp542, Arg526 and Asp443
Pinostrobin	-41.611	-41.093	-0.518	π-anion	Asp203 and Asp443
				Van der Waals	Asp203
				π-π stacking	Phe575
Panduratin A	-57.015	-47.367	-9.648	Hbonds	Asp203
				π-anion	Asp203
				π-π stacking	Phe450
				π-alkyl	Tyr299, Trp406 and Phe575

The ligand of pinostrobin and panduratin A have been successfully carried out in molecular docking tests with grid scores of –41.611 and –57.015, respectively **(Table 1)**. This value of both compounds in grid score is higher than miglitol, implying that those two compounds have lesser activity compared to miglitol. On the other hand, panduratin A, which has a lesser grid score compared to pinostrobin, interacts with hydrogen bond and π-anion to Asp203, π-π stacking to Phe450 and hydrophobic interaction to Lys480, Tyr299, Trp406 and Phe575. Panduratin A also exhibits a more prominent electrostatic with –9.648 than pinostrobin which only has –0.518. On the other hand, unlike miglitol and panduratin A, pinostrobin, has no hydrogen bond interaction to the receptor. The interaction of pinostrobin only π-anion to Asp203 and Asp443 and π-π stacked to Phe575. Therefore, it is clear that pinostrobin interaction is dominated by van der Walls interaction. The difference in the grid score values of panduratin A and pinostrobin is thought to be the influence of several interaction on both compounds. Apart from that, the difference in the respective functional groups in miglitol, which is an iminosugar that hydroxylated at the 2, 3, and 4 rings and interacts with numerous amino acids through hydrogen bonds. Miglitol's N atom is also able to form H bond to Asp443. In other ways, pinostrobin makes 2 π-anion interaction with chromane and benzene ring; while panduratin A has 2 OH groups at positions 2 and 4 that make hydrogen bonding to Asp203, moreover, methyl and prenyl functional group encounter hydrophobic interaction to several residues such as Tyr299, Trp406 and Phe575, another hydrophobic interaction also observed in the phenol-aromatic ring with Lys480 and π-π stacking of benzene ring to Phe450.

The results indicate that pinostrobin and panduratin A have higher grid scores, suggesting they may exhibit lower activity compared to the standard drug, miglitol. This is further

supported by the docking results, where miglitol forms multiple hydrogen bonds, whereas pinostrobin and panduratin A show fewer hydrogen bonds. From a 3D interaction perspective, we observe that both pinostrobin and panduratin A are unable to reach the deep binding pocket due to their bulkier structures, while miglitol fits more effectively into the pocket of the receptor **(Figure 3)**.

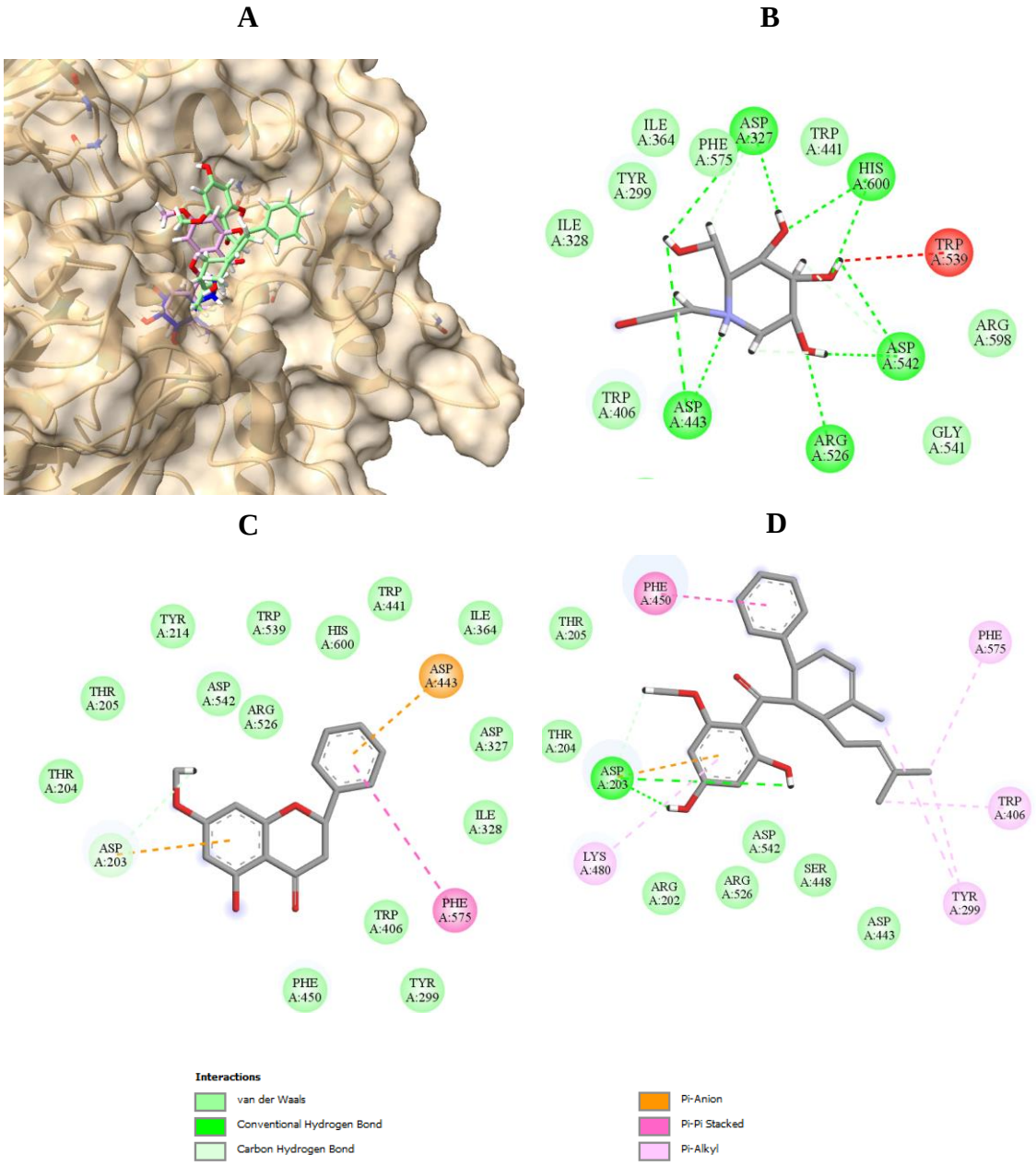

Figure 3. 3D View docking result [**Miglitol**:Blue; **Pinostrobin**:Pink; **Panduratin A**: Green](A) and 2D Interactions of **Miglitol**(B) **Pinostrobin**(C) and **Panduratin A**(D) with α-Glucosidase.

4. Conclusions

This research presents an in silico study on compounds isolated from Fingerroot for α-glucosidase inhibition (PDB ID 3L4W). Panduratin A shows limited potential for inhibiting α-glucosidase based on its grid score. It interacts with several key amino acid residues, including hydrogen bonds and π-anion interactions with Asp203, π-π stacking with Phe450, and hydrophobic interactions with Lys480, Tyr299, Trp406, and Phe575. Further studies on both pinostrobin and panduratin A are needed to enhance their α-glucosidase inhibitory potential, as well as to explore additional bioactivities.

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