

VIRTUAL SCREENING OF NATURAL ALPHA-GLUCOSIDASE INHIBITOR FROM *ALPINIA GALANGA* BIOACTIVE COMPOUNDS AS ANTI-DIABETIC CANDIDATE

Wira Eka Putra^{*1}, Sustiprijatno², Arief Hidayatullah³, Diana Widiastuti⁴, Muhammad Fikri Heikal⁵, Wa Ode Salma⁶

Address(es):

¹ Biotechnology Study Program, Department of Applied Sciences, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, East Java, Indonesia.

² Research Center for Plant Conservation, Botanic Gardens, and Forestry, National Research and Innovation Agency, Cibinong-Bogor, West Java, Indonesia.

³ Department of Biology, Faculty of Mathematics and Natural Sciences, Universitas Negeri Malang, East Java, Indonesia.

⁴ Department of Chemistry, Faculty of Mathematics and Natural Science, Universitas Pakuan, West Java, Indonesia.

⁵ Tropical Medicine International Program, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.

⁶ Department of Nutrition, Faculty of Public Health, Halu Oleo University, Indonesia.

*Corresponding author: wira.putra.fmipa@um.ac.id

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ABSTRACT

Glucose toxicity become serious risk factor of type 2 diabetes mellitus. Multiple complication can be caused of the abnormal condition of glucose level in blood. Thus, managing the plasma glucose is one of the strategy to minimize the negative effects of type 2 diabetes mellitus. In this present study, we aimed to virtually evaluate the bioactive compounds from *Alpinia galanga* as inhibitor agent against alpha-glucosidase, which was known as carbohydrate catabolic enzyme. The 2D structure of ligands were retrieved from PubChem database (pubchem.ncbi.nlm.nih.gov/) and were evaluated based on Lipinski rule of five for ensured the druglike-ness standard, while the sequence and 3D structure of target protein, alpha-glucosidase, was retrieved from UniProt database (<https://www.uniprot.org/>) and was modelled through SWISS-MODEL (swissmodel.expasy.org/). All ligands used in this study then underwent optimization prior to molecular docking and analyzing procedures. According to our prediction results, we found that galangin and 1's-1'-acetoxychavicol acetate which known as bioactive compounds found in *A. galanga* have significant potency as inhibitor agents against the alpha-glucosidase due to its binding affinity scores and other physicochemical properties compared to the anti-diabetic drug, miglitol. Thus, from this finding, we have recent starting point to expand the potency of these bioactive compounds, especially for inhibiting the alpha-glucosidase as the novel strategy to reduce the poor prognosis of type 2 diabetes mellitus.

Keywords: Alpha-glucosidase, *Alpinia galanga*, galangin, glucose toxicity, T2DM

INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) is expected to rise each year (Chintha et al., 2019; William et al., 2017). T2DM prevalence is estimated to increase approximately 439 million incidence worldwide by 2030 (Heidenreich et al., 2017). This incidence is positively correlated to the negative effect of obesity, unhealthy food and life style, and other factors (Chintha et al., 2019; Salvatore et al., 2018). On the other hand, the T2DM often followed by the increasing level of blood sugar which was known to have responsible for many other systemic diseases that causing by the glucose toxicity (Ismail et al., 2021). Another report have revealed that elevated triglyceride, blood pressure level, and lack of physical activity increase the risk factor of diabetes mellitus type 2 (Ley et al., 2018). In T2DM patient, even though pancreatic β -cells produce the insulin, however the cell fails to utilize the glucose due to the insulin resistance (Taylor, 2012; Saini, 2010). Thus, this condition increase the glucose level and concentration outside the cells. Importantly, the excessive number of sugar in blood causing multiple adverse effects such as cardiovascular diseases, hypertension, and stroke (Tun et al., 2017; Chen et al., 2016). Therefore, the strategy to minimize the glucose level in blood is necessary to encouraged.

Generally, inhibiting the glucose cumulation in blood can reduce the negative risk of T2DM. Many approaches have been done to inhibit this condition through limiting carbohydrate intake, routine exercise, and even insulin injection to the people with T2DM (Colberg et al., 2010; Hamdy et al., 2001). However, all of these strategies still uneffective and inefficient to totally combat the bad influence of T2DM. Recently, the physicians and scientists now give more attentions to target the carbohydrate-converted enzyme called alpha-glucosidase. In the normal condition, alpha-glucosidase can breakdown the carbohydrate into glucose (Kazeem et al., 2013; Bischoff, 1995), however this situation become unfavorable condition in T2DM patient. Thus, inhibiting the action of alpha-glucosidase enzyme is very important to minimize the glucose level in blood, including the use of medicinal plants.

Indonesia considered as a mega biodiversity country have a great opportunity to utilize many natural resources, including plants and animals for the raw material of pharmaceutical industries (Hidayatullah et al., 2023; Arozal et al., 2020). *A.*

galanga is one of plant that widely distributed in the tropical area, including Indonesia. *A. galanga* has been used for many purposes by local people such as food source, spices, and traditional medicine (Chouni and Paul, 2018; Silalahi, 2017). It has been reported that the *A. galanga* contain high-rich bioactive compounds including galangin, α -fenchyl acetate, β -farnesene, β -bisabolene, α -bergamotene, β -pinene, 1'S-1'-acetoxychavicol acetate, galangal acetate, and eucalyptol (Chouni and Paul, 2018). Due to its phytochemical compounds, the *Alpinia* species often used to treat several type of diseases such as cancer, inflammation, cardiovascular diseases, and even diabetes (Chouni and Paul, 2018; Ghosh and Rangan, 2013). From above explanation, then we aimed to virtually evaluate the therapeutic potency of *A. galanga* bioactive compounds as inhibitory agents against the alpha-glucosidase as target protein.

MATERIAL AND METHODS

Bioactive compounds were used in this study such as galangin (CID: 5281616), α -fenchyl acetate (CID: 6427102), β -farnesene (CID: 5281517), β -bisabolene (CID: 10104370), α -bergamotene (CID: 86608), β -pinene (CID: 14896), 1'S-1'-acetoxychavicol acetate (CID: 119104), galangal acetate (CID: 400072), and eucalyptol (CID: 2758). Additionally, the control drug, miglitol (CID: 441314) used to compare the binding site and binding affinity efficiency. All the chemicals were retrieved from PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) and were evaluated based on the Lipinski rule of five in order to ensure druglikeness via Supercomputing Facility for Bioinformatics and Computational Biology website, IIT Delhi (<http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp>). Furthermore, for the 3D protein structure of alpha-glucosidase was built via SWISS-MODEL (<https://swissmodel.expasy.org/>). The 3D structure of alpha-glucosidase as target protein was optimized by cleaning the residual ligands, adding the hydrogen atom and polarity on the structure. Protein binding site analysis were performed before ligands and docking simulation. From that step, the binding space and coordinate were set as X=-1.9699, Y=-22.2793, and Z=-21.5264 on the PyRx software (<https://pyrx.sourceforge.io/>). Finally, molecular docking simulation and visualization were assessed as our previous protocols (Hidayatullah et al., 2023; Putra et al., 2021).

RESULTS AND DISCUSSION

Targeting the alpha-glucosidase in order to minimize the blood sugar level will help in decreasing the adverse effect of T2DM (Cai et al., 2013; Derosa and Maffioli, 2012). As the inhibition reaction, the alpha-glucosidase will stop its activity in converting carbohydrate into glucose (Etsassala et al., 2019; Cai et al., 2013). In this study, we have predicted the protein – ligands interaction and its physicochemical properties between the alpha glucosidase as target protein and *A. galanga* bioactive compounds, namely galangin, α -fenchyl acetate, β -farnesene, β -bisabolene, α -bergamotene, β -pinene, 1'S-1'-acetoxychavicol acetate, galangal acetate, and eucalyptol.

Based on the computational prediction, we found that galangin have the most significant binding affinity toward the alpha-glucosidase with binding affinity scores about -6.9 kcal/mol. In the second place is followed by the 1'S-1'-acetoxychavicol acetate with binding affinity scores about -6.0 kcal/mol (Figure 1). Compared to the control drug as positive control, the miglitol have binding affinity about -5.2 kcal/mol to the target protein (Table 1). The favorable interaction scores for binding affinity is determine by the negative value of those binding. The more negative of binding affinity score, the more significant that protein-ligand have stable and great interaction (Putra et al., 2023; Pantsar and Poso, 2018; Du et al., 2016).

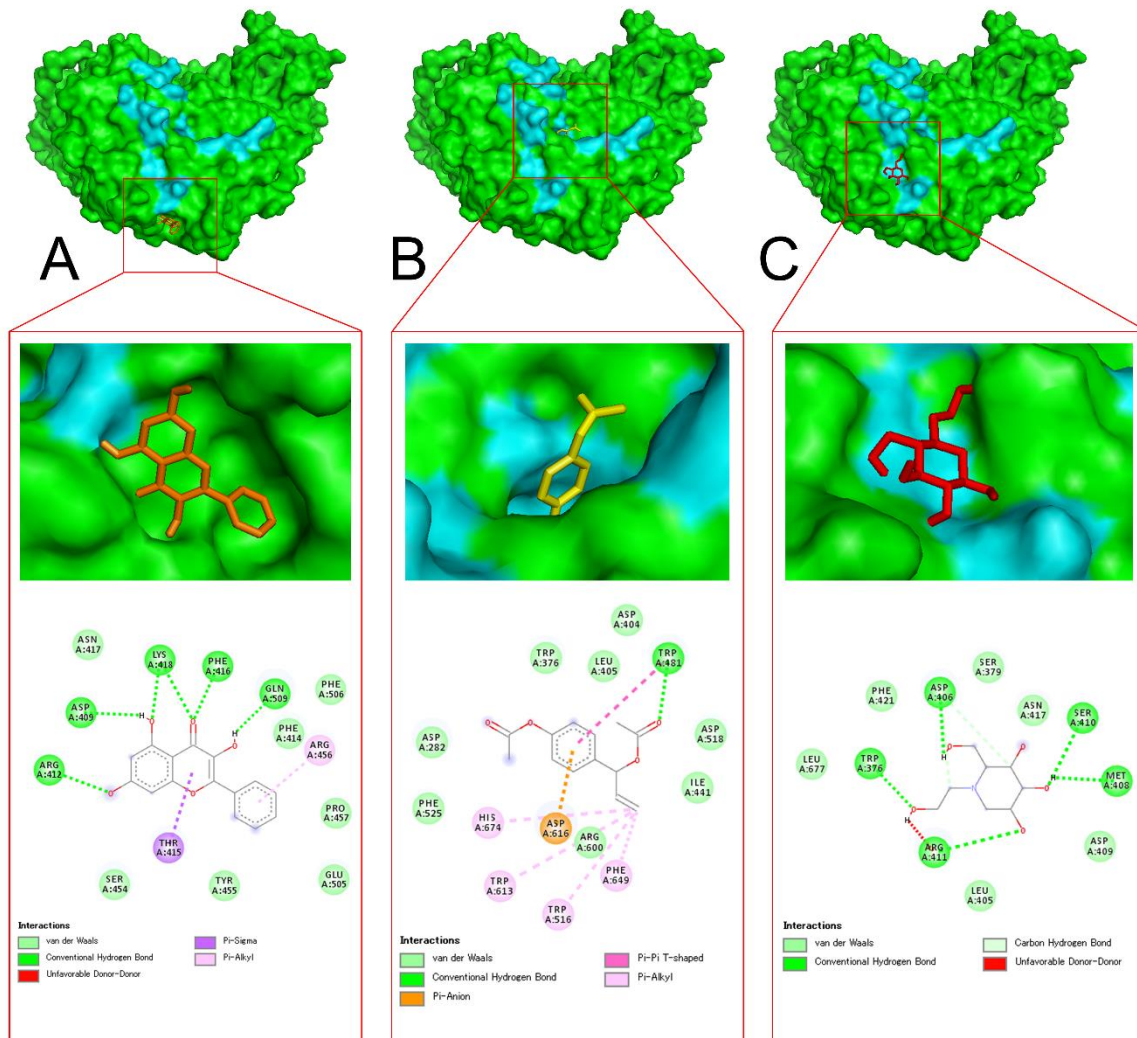


Figure 1 Protein – ligand interaction between the alpha –glucosidase and (A) galangin, (B) 1'S-1'-acetoxychavicol acetate, and (C) miglitol. Green color refers to whole structure of alpha – glucosidase, and cyan color refers to the binding and active site region.

Alpha-glucosidase - galangin complex chemical interaction includes van der Waals, conventional hydrogen bond, pi-sigma, and pi-alkyl; Alpha-glucosidase - 1'S-1'-acetoxychavicol acetate complex chemical interaction includes van der Waals, conventional hydrogen bond, pi-pi t-shaped/ pi-alkyl, and pi-anion; and Alpha-glucosidase - miglitol complex chemical interaction includes van der Waals, conventional hydrogen bond, and carbon hydrogen bond. Further, in each particular chemical interaction, there will be amino acid residues which were used to identify the binding site area and also used to determine the binding characters (Table 1). In this present study, we also evaluate the other physicochemical properties of protein – ligand complexes, including hydrophobicity, H-bonds, interpolated charge, and ionizability (Figure 2).

Recent trend in the health and medicine field is utilizing the medicinal herb as main drug component or supplementary medicine to combat several type of diseases, including diabetes mellitus (Hidayatullah et al., 2023; Chouni and Paul, 2018; Ghosh and Rangan, 2013). *A. galanga* known for its rhizome which was used as spices, food sources, and also traditional medicine by common citizen (Chouni and Paul, 2018; Silalahi, 2017). Interestingly, it has been reported that *A. galanga* widely used for therapeutic purposes as anti-diabetic, immunomodulator, anti-cancer, anti-inflammatory, anti-oxidant, hepato-protective, cardio-protective, and neuro-protective (Chouni and Paul, 2018; Ghosh and Rangan, 2013). This therapeutic potency of *A. galanga* to cure diseases expectedly due to its bioactive-rich compound (Chouni and Paul, 2018).

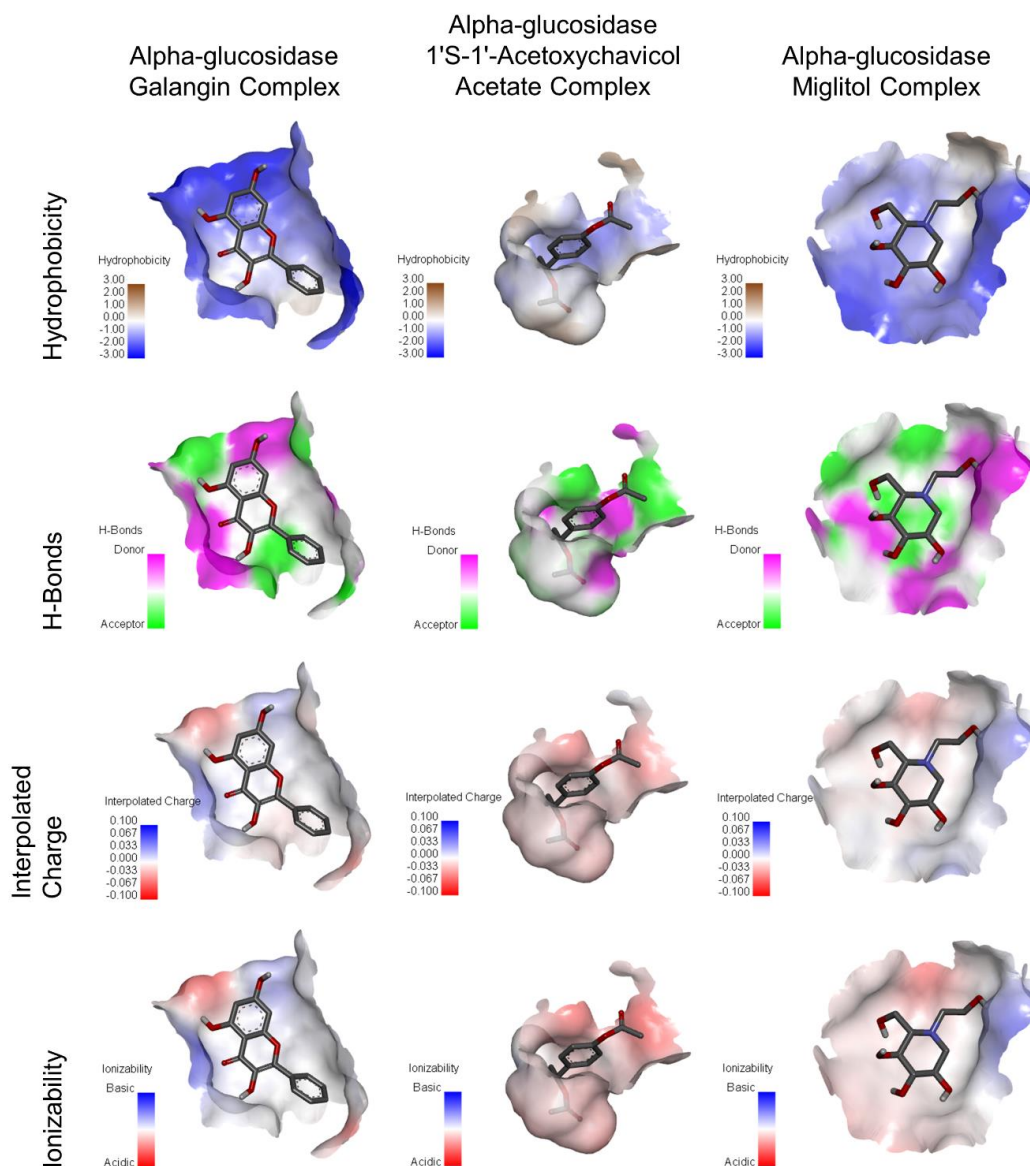


Figure 2 Physicochemical properties of target protein and ligands binding of alpha-glucosidase - galangin complex, alpha-glucosidase - 1'S-1'-acetoxychavicol acetate complex, and alpha-glucosidase - miglitol complex. The physicochemical properties measured in this study including hydrophobicity, H-bonds, interpolated charge, ionizability.

Table 1 The protein and ligands complex properties including binding affinity, chemical interactions, and amino acid residue

No.	Complex	Binding Affinity	Chemical Interaction	Amino Acid Residu
1.	Alpha-glucosidase - Galangin	-6.9 kcal/mol	Van der Waals	ASN A:417, PHE A:506, PHE A:414, PRO A:457, GLU A:505, TYR A:455, SER A:454
			Conventional Hydrogen Bond	ARG A:412, ASP A:409, LYS A:418, PHE A:416, GLN A:509
			Pi-Sigma	THR A:415
			Pi-Alkyl	ARG A:456
2.	Alpha-glucosidase - 1'S-1'-Acetoxychavicol Acetate	-6.0 kcal/mol	Van der Waals	PHE A:525, ASP A:282, TRP A:376, LEU A:405, ASP A:404, ASP A:518, ILE A:441, ARG A:600
			Conventional Hydrogen Bond	TRP A:481
			Pi-Pi T-shaped/ Pi-Alkyl	HIS A:674, PHE A:649, TRP A:516, TRP A:613
			Pi-Anion	ASP A:616
3.	Alpha-glucosidase - Miglitol	-5.2 kcal/mol	Van der Waals	LEU A:677, PHE A:421, SER A:379, ASN A:417, ASP A:409, LEU A:405
			Conventional Hydrogen Bond	TRP A:677, ASP A:406, SER A:410, MET A:408, ARG A:411
			Carbon Hydrogen Bond	ASP A:406

On the other hand, we showed that galangin might have great potency as inhibitor agent for alpha-glucosidase. Galangin or 3,5,7-trihydroxyflavone is a flavonol, a group of flavonoid. According to several reports, galangin has been used for long time for medicinal purposes due to its biological activities such as anti-fibrotic, anti-mutagenic, anti-tumor, anti-bacteria, and antioxidant effect (Lee et al., 2017;

Zhang et al, 2010). A study also showed the potency of honey which contained galangin successfully enhanced glucose metabolism in STZ-induced diabetic mice (Ding et al., 2019).

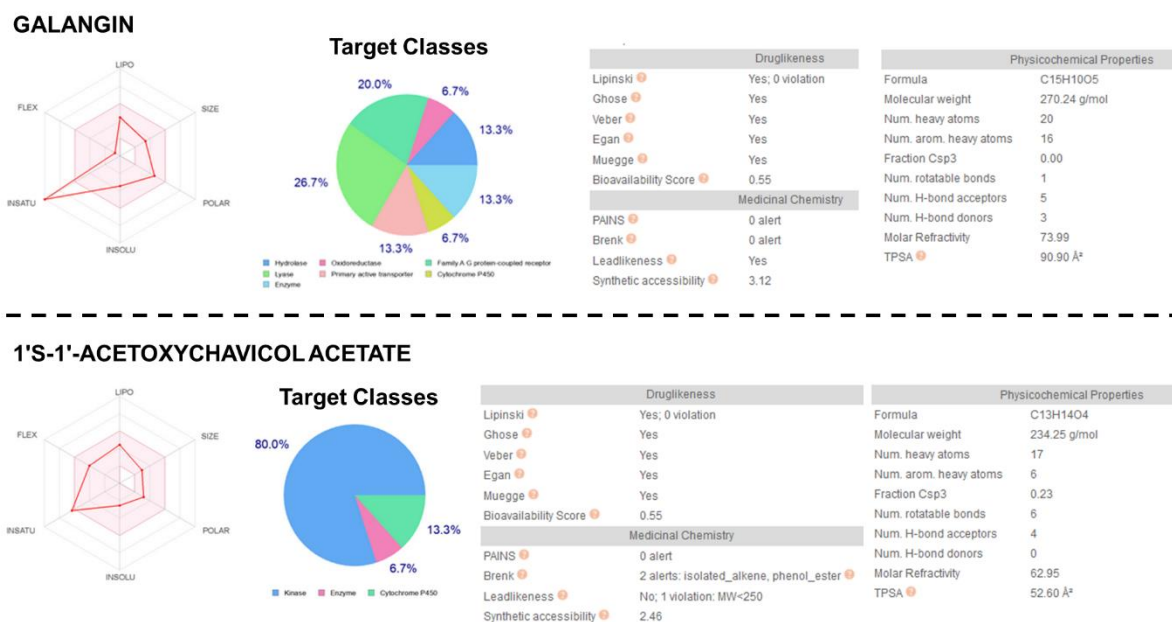


Figure 3 The general features of galangin and 1'S-1'-acetoxychavicol acetate. The figures showed basic information of physicochemical properties, target protein classes, druglikeness, and medicinal chemistry.

Another study also showed the anti-diabetic effect of galangin reverted the plasma glucose into normal condition and reduced the hyperlipidaemic in diabetic rats model (Aloud et al., 2018). These previous evidences showed the strong prospective potency of galangin as alpha-glucosidase inhibitor. Furthermore, we evaluated two compound which have the greatest binding affinity, galangin and 1'S-1'-acetoxychavicol acetate according to its potential as druglikeness and medicinal chemistry properties (Figure 3).

CONCLUSION

Finally, according to our computation simulation, again we predict that galangin (-6.9 kcal/mol) and 1'S-1'-acetoxychavicol acetate (-6.0 kcal/mol) have potency as anti-diabetes agents regarding their binding affinity scores and chemical interactions pattern. More exploration about the potency of bioactive compounds from *A. galanga* is necessary, especially for the *in vivo* or *in vitro* study to evaluate the biological mechanism of those bioactive compounds.

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