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Computational assessment of hypoglycemic potency and ADMET evaluation of *Alpinia galanga* bioactive compounds against the alpha-glucosidase enzyme

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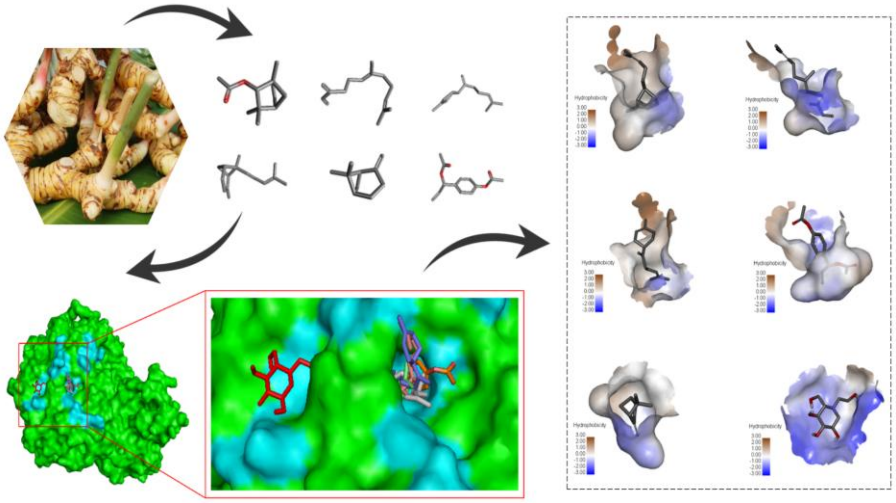
Abstract

Alpha-glucosidase is known as a catabolic enzyme for carbohydrates which determine the glucose level in body. Therefore, inhibiting the activity of alpha-glucosidase should reduce the glucose plasma level. Thus, we aimed to evaluate the antidiabetic potency of bioactive *Alpinia galanga* compounds against alpha-glucosidase through an *in silico* approach. To a greater extent, the 2D structure of the ligands was retrieved from the PubChem database, and the 3D structure of alpha-glucosidase was built on the SWISS-MODEL website. Furthermore, pharmacokinetics analysis was performed via the pkCSM webserver. Interestingly, we showed that the potential interactions of α-bergamotene, β-farnesene, β-bisabolene, galangal acetate, and β-pinene were more significant than those of miglitol within the binding site region of alpha-glucosidase. This present study demonstrated that numerous bioactive compounds of *Alpinia galanga* have potential as antidiabetic agents based on the molecular docking and pharmacokinetics prediction. Thus, we suggest that the bioactive compounds of *Alpinia galanga* may be effective as alpha-glucosidase inhibitors. However, further comprehensive studies are needed to evaluate their biological effects, effectiveness, and efficacy.



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Section Editors

Boutros **Sarrouh**

Highlights

- Glycemic management is a key factor in inhibiting the effect of diabetes mellitus 2.
- Blood glucose levels can be reduced by inhibiting the activity of alpha-glucosidase.
- The bioactive compounds of *Alpinia galanga* have antidiabetic effects.

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1. Introduction

The International Diabetes Federation estimated that 463 million people worldwide had diabetes in 2019. In the absence of effective preventive measures, the number is projected to increase to 578 million by 2030 and 700 million by 2045. Importantly, the average lifespan is reduced by approximately ten years due to type 2 diabetes mellitus (T2DM). Glycemic management is one of the crucial key factors in inhibiting the undesired effects of T2DM (Perlmuter *et al.*, 2008; Seley *et al.*, 2014). T2DM is a typical systemic disease, which means that the negative side effects of this disease can directly or indirectly affect other biological systems. Numerous problems are more common in people with type 2 diabetes, primarily because of intricately linked mechanisms such as low-grade inflammation, insulin resistance, high blood sugar levels, and increased atherogenesis. Furthermore, the symptoms of type 2 diabetes mellitus typically include nocturia, polyuria, polydipsia, polyphagia, intense hunger, weight loss, fatigue, lack of interest and foc us, vomiting, stomach pain, blurred vision, common infections and inflammation, and discomfort in the extremities (Ewing *et al.*, 2010; Farmaki *et al.*, 2020). Interestingly, high levels of glucose plasma can induce multiple disorders or organ complications, such as cardiovascular diseases, obesity, stroke, and hypertension (Campos, 2012; Kawahito *et al.*, 2009).

Although there is currently no known cure for this condition, treatment options include changing lifestyle habits, managing obesity, taking oral hypoglycemic medications, and using insulin sensitizers or biguanides that lower insulin resistance. Several modalities have been proposed to reduce the glucose level in the blood, such as body exercise, diet control, insulin injection, and other medical treatments (Asif *et al.*, 2014; Colberg *et al.*, 2010). Furthermore, the current trend in anti-diabetic research is the targeting of certain potential molecules or factors, such as alpha-glucosidase, an enzyme that converts dietary carbohydrates into glucose, to minimize the worst possibility caused by diabetes. The pancreatic enzyme family known as alpha-glucosidase is involved in the conversion of most of the carbohydrates ingested into glucose. After being absorbed into the bloodstream, this glucose causes frank postprandial hyperglycemia, which aggravates diabetes patients' symptoms and leads to problems. Thus, it has been postulated that the glucose level in the blood can be reduced by inhibiting the activity of alpha-glucosidase. Although type 2 diabetes is thought to be more effectively controlled with alpha-glucosidase inhibitors, these commercially accessible drugs have several disadvantages, including high costs and noncompliance from patients (Derosa *et al.*, 2012; Van de Laar *et al.*, 2005). As a result, the development of new medications to treat diabetes mellitus is essential.

The use of traditional medicine has increased over time due to its various medicinal properties (Oyebode *et al.*, 2016; Putra and Rifa'i, 2019; Putra and Rifa'i, 2020a; Putra *et al.*, 2023; Zank *et al.*, 2017). Other than that, the consideration of medicinal plants for therapeutic agents because of their medicinal potential is safer, more economical, and easier to find (Katiyar *et al.*, 2012). In Indonesia, the use of traditional medicine was shown for a long time by local tribes. *Alpinia galanga* is a common plant used in Indonesia as a food source, spice, and home remedy. *Alpinia galanga*, which belongs to the Zingiberaceae family, is commonly referred to as galangal. It has been widely utilized for its emmenagogue, aphrodisiac, abortifacient, carminative, antipyretic, and anti-inflammatory properties. It has also been utilized in the treatment of a variety of diseases, including bronchitis, heart diseases, chronic enteritis, renal calculus, diabetes, rheumatism, and kidney disorders. Essential oils, tannins, phenols, glycosides, monoterpenes, and carbohydrates have been reported to be among the components that are present in these products (Kaushik *et al.*, 2011). To a greater extent, *Alpinia galanga* contains several bioactive compounds, including α-bergamotene, β-bisabolene, α-fenchyl acetate, β-farnesene, β-pinene, and galangal acetate. Interestingly, *Alpinia galanga* has potential anticancer, antidiabetic, anti-inflammatory, antioxidant, cardioprotective, hepatoprotective, immunomodulator, and neuroprotective effects (Chouni and Paul, 2018). Thus, from the above explanation, we aimed to evaluate the antidiabetic potency of *the* bioactive compounds of Alpinia galanga as inhibitors of alpha-glucosidase through an *in silico* approach.

2. Experimental

2.1. Ligand structure retrieval

Alpinia galanga was subjected to further exploration of its bioactive compounds, especially its antidiabetic activity, by inhibiting alpha-glucosidase. Five common bioactive compounds widely found in *Alpinia galanga* were evaluated: α-fenchyl acetate (CID: 6427102), β-farnesene (CID: 5281517), β-bisabolene (CID: 10104370), α-bergamotene (CID: 86608), β-pinene (CID: 14896), and galangal acetate (CID: 400072). The 2D structures of these compounds were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Furthermore, to ensure the binding quality of the compounds, miglitol (CID: 441314), an alpha-glucosidase inhibitor, was used as the control drug. Finally, each ligand is transferred to a sdf. filing format for the files to be compatible with the data reading capabilities of docking software.

2.2. Protein homology modeling

Alpinia galanga was subjected to further exploration of its bioactive compounds, especially its antidiabetic activity, by inhibiting alpha-glucosidase. Five common bioactive compounds widely found in *Alpinia galanga* were evaluated: α-fenchyl acetate (CID: 6427102), β-farnesene (CID: 5281517), β-bisabolene (CID: 10104370), α-bergamotene (CID: 86608), β-pinene (CID: 14896), and galangal acetate (CID: 400072). The 2D structures of these compounds were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). Furthermore, to ensure the binding quality of the compounds, miglitol (CID: 441314), an alpha-glucosidase inhibitor, was used as the control drug. Finally, each ligand is transferred to a sdf. filing format for the files to be compatible with the data reading capabilities of docking software (Putra and Rifa'i, 2020b).

2.3. Molecular docking simulation

Molecular docking and visualization of the target protein and ligand complexes were performed according to our previous methods (Hidayatullah *et al.*, 2022; Hidayatullah *et al.*, 2021a). PyRx software (https://pyrx.sourceforge.io/) was used to perform molecular docking targeting alpha-glucosidase with the various ligands from *Alpinia galanga* mentioned above with non-solvent

model by removing water from structure of protein. The visualization of the molecular docking data was then performed via BIOVIA software (https://discover.3ds.com) to demonstrate the binding pattern, amino acid residues, and hydrophobicity of the protein–ligand complex.

2.4. Absorption, distribution, metabolism, excretion, and toxicity analysis

In the present study, we predicted the small-molecule pharmacokinetic properties via the pkCSM - Biosig Lab webserver (https://biosig.lab.uq.edu.au/pkcsm/). The pharmacokinetic parameters, including the absorption, distribution, metabolism, excretion, and toxicity features of the bioactive compounds of *Alpinia galanga*, were evaluated.

3. Results and discussion

Under normal conditions, alpha-glucosidase plays an important role in carbohydrate metabolism. This enzyme is responsible for completing and supplying the glucose needed by the cells which could be used for other biological activities (Kim *et al.*, 2012; 2017). However, in the case of T2DM, the function of alpha-glucosidase needs to be reduced because catabolic activity can worsen this condition and is often followed by complications in several organs (Oguntibeju, 2019; Zhang *et al.*, 2019). Thus, in this study, we virtually targeted alpha-glucosidase with bioactive compounds from *Alpinia galanga* which previously shown to have therapeutic potencies in treating multiple ailments, including diabetes mellitus (Fig. 1).

A variety of oral hypoglycemic agents are currently available, each targeting different pathways involved in glucose metabolism. Nevertheless, oral medications known as alpha-glucosidase inhibitors have demonstrated efficacy in both preventing and treating diabetes. By inhibiting intestinal alpha-glucosidase in an adversarial and reversible manner, these inhibitors can reduce postprandial glycemia. This is accomplished by delaying the digestion of carbohydrates and reducing the rate at which glucose is absorbed (Agrawal *et al.*, 2022; Lu *et al.*, 2023). Acarbose, voglibose, and miglitol are the three alpha-glucosidase inhibitors that have been approved for clinical use in recent years. Unfortunately, these alpha-glucosidase inhibitors based on carbohydrate mimics have limited therapeutic uses because of their unwanted side effects which might harm the patients' condition (Cai *et al.*, 2023; Dirir *et al.*, 2022). Therefore, the identification of new drug candidates for preventing and treating diabetes mellitus is necessary and important.

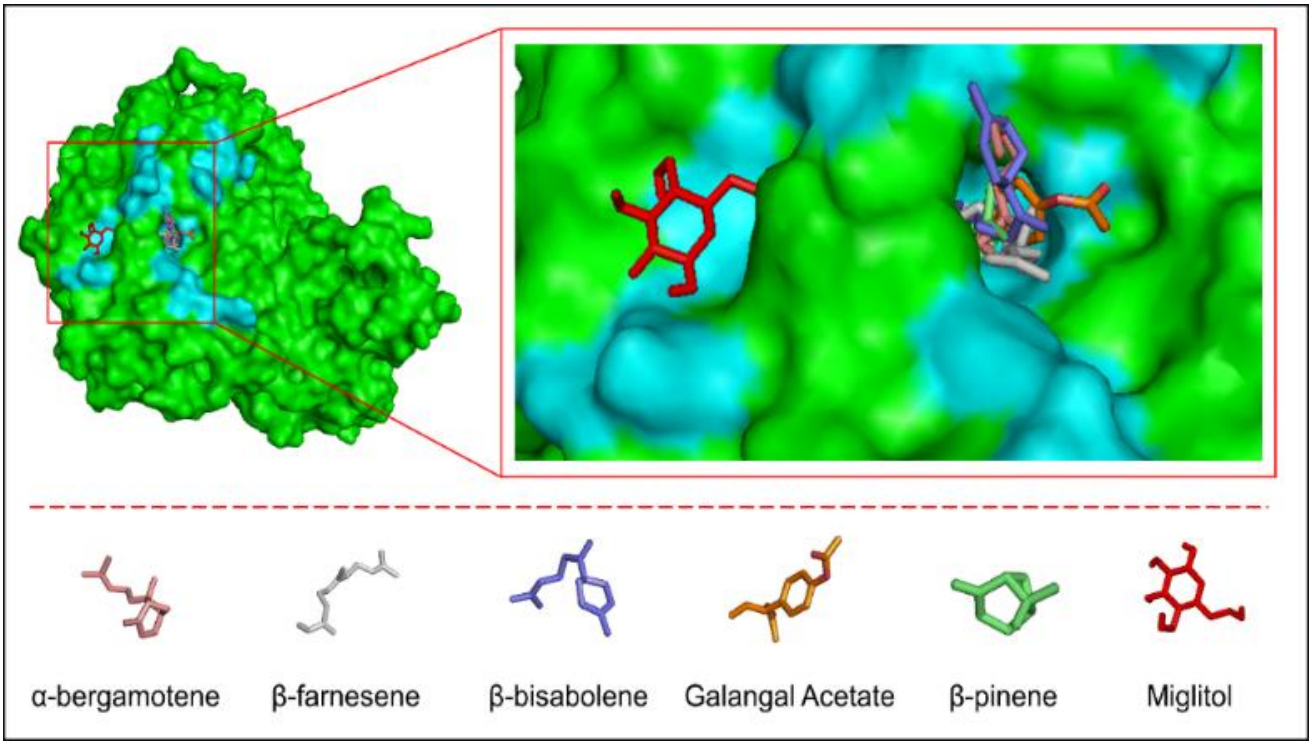

Figure 1. The ligands interacted with the target protein in the same binding site region of the target protein (alpha-glucosidase), except miglitol, which was used as the control drug. The green color indicates the whole protein structure; the cyan color indicates the binding site region of AG.
Source: Elaborated by the authors.

According to our prediction, the bioactive compounds of *Alpinia galanga* have significant binding affinities compared with those of the control drug, i.e., the alpha-glucosidase-α-bergamotene complex (–24.7 kJ/mol), the alpha-glucosidase-β-farnesene complex (–24.7 kJ/mol), the alpha-glucosidase-β-bisabolene complex (–24.3 kJ/mol), the alpha-glucosidase-gal acetate complex (–23.4 kJ/mol), the alpha-glucosidase-β-pinene complex (–22.2 kJ/mol), and the alpha-glucosidase-miglitol complex (–21.8 kJ/mol) (Table 1). Studies have shown that more negative binding affinity scores indicate that the ligands have a greater chance of having favorable and stable interactions with the target protein (Du *et al.*, 2016; Hidayatullah *et al.*, 2021b; Pantsar and Poso, 2018; Putra, 2018; Widiastuti *et al.*, 2024). These initial findings suggested that the bioactive compounds of *Alpinia galanga* might have potential as drug candidates for treating diabetes mellitus, especially via the inhibition of alpha-glucosidase activity.

On the other hand, we examined the hydrophobicity properties of each complex interaction, as shown in **Fig. 2**. Furthermore, we also showed the chemical interaction pattern of each protein–ligand complex, namely, the alpha–glucosidase–α–bergamotene complex (van der Waals, pi–sigma, pi–alkyl/alkyl); the alpha–glucosidase–β–farnesene complex (van der Waals, pi–sigma, pi–alkyl/alkyl); the alpha–glucosidase–β–bisabolene complex (van der Waals, pi–sigma, pi–alkyl/alkyl); the alpha–glucosidase–galangal acetate complex (van der Waals, pi–sigma, pi–alkyl, pi–sulfur, pi–anion); the alpha–glucosidase–β–pinene complex (van der Waals, pi–alkyl/alkyl); and the alpha–glucosidase–miglitol complex (conventional hydrogen bonding, carbon–hydrogen bonding, van der Waals) (**Fig. 3**). Additionally, all the bioactive compounds bind to the target protein in the same area of the binding site.

Table 1. The list of binding affinity scores, chemical interaction types, and amino acid residues of each protein–ligand complex.

Complex	Binding Affinity (kJ/mol)	Chemical Interaction	Amino Acid Residue
Alpha-glucosidase-α-bergamotene	−24.7 kJ/mol	van der Waals	ASP A:404, ASP A:518, ARG A:600, ASP A:616, LEU A:650, SER A:676
		Pi-Sigma	TRP A:376
		Pi-Alkyl/Alkyl	LEU A:405, TRP A:481, MET A:519, PHE A:649
Alpha-glucosidase-β-farnesene	−24.7 kJ/mol	van der Waals	ASP A:404, ILE A:441, ASP A:518, MET A:519, ARG A:600, ASP A:616
		Pi-Sigma	PHE A:525
		Pi-Alkyl/Alkyl	TRP A:376, LEU A:405, TRP A:481, TRP A:516, PHE A:649, HIS A:674
Alpha-glucosidase-β-bisabolene	−24.3 kJ/mol	van der Waals	ASP A:404, ILE A:441, ARG A:600, ASP A:616, LEU A:650, SER A:676, LEU A:678.
		Pi-Sigma	TRP A:376
		Pi-Alkyl/Alkyl	LEU A:405, TRP A:481, TRP A:516, PHE A:649, HIS A:674
Alpha-glucosidase-Galangal Acetate	−23.4 kJ/mol	van der Waals	ALA A:284, ASP A:404, LEU A:405, ILE A:441, TRP A:481, ASP A:518, ARG A:600, TRP A:613
		Pi-Sigma	TRP A:376
		Pi-Alkyl	TRP A:516, PHE A:649, HIS A:674
		Pi-Sulfur	MET A:519
		Pi-Anion	ASP A:616
Alpha-glucosidase-β-pinene	−22.2 kJ/mol	van der Waals	ASP A:404, LEU A:405, ILE A:441, TRP A:516, ASP A:518, ARG A:600, TRP A:613, ASP A:616
		Pi-Alkyl/Alkyl	TRP A:376, TRP A:481, MET A:519, PHE A:648, HIS A:674
Alpha-glucosidase-Miglitol	−21.8 kJ/mol	Conventional Hydrogen Bond	ASP A:406, MET A:408, SER A:410, ARG A:411, TRP A:677
		Carbon Hydrogen Bond	ASP A:406
		van der Waals	SER A:379, LEU A:405, ASP A:409, ASN A:417, PHE A:421, LEU A:677

Source: Elaborated by the authors.

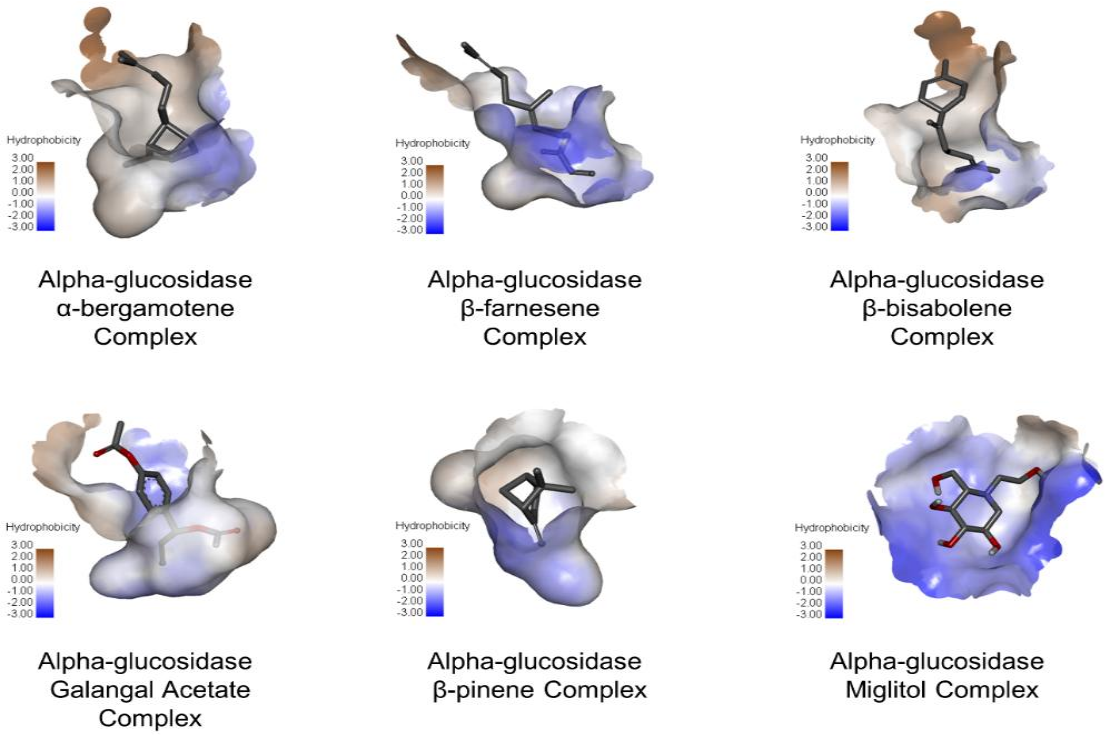

Figure 2. The hydrophobicity properties of each protein–ligand interaction. The color around the ligand indicates the hydrophobicity score.
Source: Elaborated by the authors.

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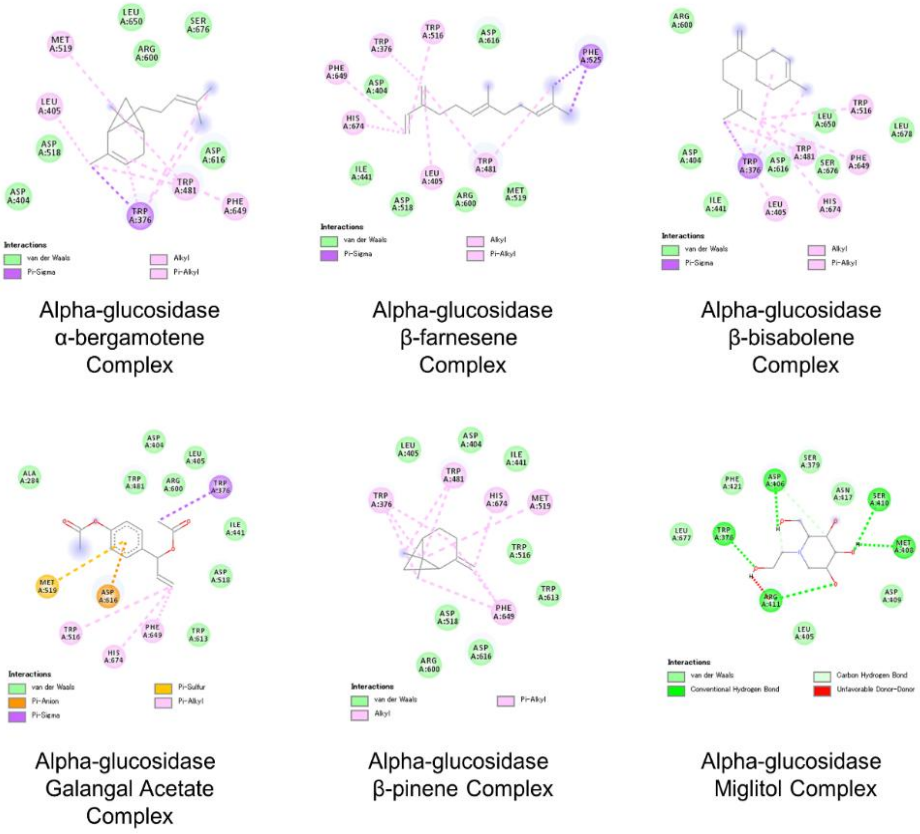

Figure 3. Two-dimensional interaction between the ligand and protein. This schematic shows the interaction type with certain amino acid residues from the target protein.
Source: Elaborated by the authors.

The mechanism of action of these potential compounds requires further investigation to precisely define their effects, particularly in relation to their antidiabetic activity against α-glucosidase. Interestingly, several studies have demonstrated multiple advantages of *Alpinia galanga*, especially for therapeutic purposes, such as its antidiabetes effects, ability to ameliorate cold, ability to clear the circulatory system, and ability to reduce swelling and stomachache (Chouni and Paul, 2018; Verma *et al.*, 2015). Research conducted by Arambewela *et al.* (2009) demonstrated that *Alpinia galanga* has an antidiabetic effect on streptozotocin-induced diabetic rats by inhibiting glucose absorption in the small intestine and promoting the accumulation of glycogen in the liver and muscle. Furthermore, another study reported the hypoglycemic activity of the *Alpinia galanga* rhizome in rabbits. This experiment revealed that powdered rhizomes, methanol, and aqueous extracts can lower the plasma glucose level in normal rabbits (Akhtar *et al.*, 2002). The mechanism of action for reducing glucose levels in the blood varies, one of which involves the inhibition of alpha-glucosidase, which is known as a carbohydrate catabolic enzyme (Yin *et al.*, 2014). Therefore, the identification of new potential alpha-glucosidase inhibitors needs to be improved.

The water solubility of a compound indicates how soluble a molecule is in water at 25 °C. Particularly when a compound is administered through the digestive tract, lipid-soluble drugs are less well absorbed than are water-soluble drugs. Absorption, distribution, metabolism, excretion, and toxicity analysis of *Alpinia galanga* bioactive compounds were investigated and results are in **Table 2**.

As a result, we found that the five bioactive compounds of *Alpinia galanga* are considered to have high Caco-2 permeability because they have predicted values greater than 0.90. Importantly, a compound with low intestinal absorption was determined if the absorption value was less than 30%, and good intestinal absorption was determined if the predicted value was greater than 80%. Furthermore, VDss distribution attributes are classified into the high category, with values greater than 0.45, and the low category, with values less than –0.15. In our findings, we demonstrated that all the compounds, except for galangal acetate, have high blood–brain barrier penetration because the predicted values of the compounds are greater than 0.3 log BB. Similarly, these compounds have great central nervous system permeability, except for β-bisabolene and galangal acetate. The CNS is thought to be penetrated by a compound with a log PS of more than –2, and these compounds have excellent CNS penetration. *Alpinia galanga* compounds were shown to have no discernible influence on metabolism or no contraindication mechanisms since they are not CYP3A4 substrates except α-bergamotene. The clearances of the compounds were less than 2 mL/min/kg, indicating that the compounds have a long half-life and can be cleared by the excretion organs. All the compounds had no effect on hepatotoxicity. The maximum tolerated dose for humans can be used to measure toxicity properties. The results revealed that *Alpinia galanga* compounds, except for galangal acetate, are classified as low because the predicted value is lower than 0.477 log (mg/kg/day) (Pires *et al.*, 2015; Widiastuti *et al.*, 2023).

Table 2. Absorption, distribution, metabolism, excretion, and toxicity analysis of *Alpinia galanga* bioactive compounds.

Property	Model Name	Predicted Value					Unit
		α-bergamotene	β-farnesene	β-bisabolene	galangal acetate	β-pinene	
Absorption	Water solubility	−5.97	−6.96	−6.06	−2.74	−4.19	log mol/L
	Caco2 permeability	1.40	1.41	1.42	1.33	1.39	log Papp in 10^{-6} cm/s
	Intestinal absorption (human)	96.23	93.43	95.23	95.45	95.53	% Absorbed
Distribution	VDss (human)	0.86	0.57	0.63	−0.22	0.69	log L/kg
	BBB permeability	0.86	0.84	0.79	0.09	0.82	log BB
	CNS permeability	−1.99	−1.67	−2.13	−2.37	−1.86	log PS
Metabolism	CYP3A4 substrate	Yes	No	No	No	No	Yes/No
	CYP3A4 inhibitor	No	No	No	No	No	Yes/No
Excretion	Total Clearance	1.18	1.83	1.46	0.56	0.03	log ml/min/kg
	Renal OCT2 substrate	No	No	No	No	No	Yes/No
Toxicity	Max. tolerated dose (human)	0.08	0.20	0.42	1.01	0.37	log mg/kg/day
	Oral Rat Acute Toxicity (LD50)	1.68	1.47	1.64	2.35	1.67	mol/kg
	Hepatotoxicity	No	No	No	No	No	Yes/No

Source: Elaborated by the authors.

4. Conclusions

Numerous bioactive compounds from *Alpinia galanga* show potential as antidiabetic agents due to their ability to inhibit alpha-glucosidase activity. In this study, our simulations revealed that α-bergamotene, β-farnesene, β-bisabolene, galangal acetate, and β-pinene exhibited stronger interactions within the alpha-glucosidase binding site compared to miglitol. Based on these findings, we suggest that these bioactive compounds may serve as effective alpha-glucosidase inhibitors. However, further comprehensive studies are needed by incorporating solvent models, molecular dynamics simulation, and to evaluate their biological effects, effectiveness, and efficacy.

Authors' contribution

Conceptualization: Wira Eka Putra; Sustiprijatno; Arief Hidayatullah; **Data curation**: Diana Widiastuti; Muhammad Fikri Heikal; **Formal Analysis**: Wira Eka Putra; Arief Hidayatullah; **Funding acquisition**: Wira Eka Putra; **Investigation**: Wira Eka Putra; Sustiprijatno; Arief Hidayatullah; **Methodology**: Wira Eka Putra; Arief Hidayatullah; Diana Widiastuti; Muhammad Fikri Heikal; **Project administration**: Wira Eka Putra; **Resources**: Wira Eka Putra; **Software**: Wira Eka Putra; Arief Hidayatullah; Diana Widiastuti; Muhammad Fikri Heikal; **Supervision**: Wira Eka Putra; Sustiprijatno; **Validation**: Diana Widiastuti; Muhammad Fikri Heikal; **Visualization**: Arief Hidayatullah; Muhammad Fikri Heikal; **Writing – original draft**: Wira Eka Putra; Sustiprijatno; Arief Hidayatullah; **Writing – review & editing**: Wira Eka Putra; Arief Hidayatullah; Diana Widiastuti; Muhammad Fikri Heikal

Conflict of interest

The authors declare that there is no conflict of interest.

Data availability statement

The data will be available upon request.

Artificial Intelligence usage statement

The authors declare that they did not use Artificial Intelligence tools at any stage of the preparation, correction, or evaluation of this work.

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