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In Silico Assessment of Chemical Constituents of *Zingiber officinale* Rosc. For Anti-diabetic Activity: Molecular Docking with α-Glucosidase Receptor

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Abstract: Diabetes Mellitus (DM) is a disease in which blood sugar (glucose) levels are elevated because the body cannot release or utilize insulin adequately. Rhizome of *Zingiber officinale* Rosc. (ginger) has been reported to possess anti-diabetic properties. This study aimed to provide information on the chemical components of ginger that have potential *in silico* antidiabetic activity against the α-glucosidase receptor. Twenty chemical components of ginger (quercetin, catechin, humulene, β-sesquiphellandrene, camphene, farnesene, β-sitosterol, stigmasterol, curcumin, 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, 8-shogaol, 10-shogaol, 6-paradol, 8-paradol, 10-paradol, methyl-6-gingerol, and methyl-8-gingerol) were used as ligands. An *in silico* study was conducted using the molecular docking technique with the AutoDock Vina software, which was then displayed using PyMOL and Biovia Discovery Studio. The grid box settings obtained in this study were as follows: center_x = -20.209, center_y = -6.763, center_z = 9.393, size_x = 12, size_y = 10, size_z = 12, and spacing (angstrom) = 1. The results indicated that the native ligand acarbose exhibited a binding energy of -6.9 kcal/mol. In contrast, four test ligands, quercetin (-7.3 kcal/mol), catechin (-7.1 kcal/mol), curcumin (-7.0 kcal/mol), and 6-gingerol (-7.0 kcal/mol) - demonstrated lower binding energies than acarbose, suggesting more stable conformations and more potent pharmacological effects. Lipinski analysis revealed that these four test ligands met all five Lipinski rule criteria. The study calculated the Root Mean Square Deviation (RMSD) value for the Docking of acarbose with the α-glucosidase macromolecule, resulting in a value of 0.384 Å. Interaction analysis conducted using Biovia Discovery Studio software revealed various interaction types, including hydrogen bonding, hydrophobic, electrostatic, and unfavorable interactions. In conclusion, this study provides valuable insights into potential therapeutic compounds derived from ginger and offers a foundation for further research and development in pharmaceutical and medicinal chemistry.

Keywords: α-glucosidase, diabetes, *molecular docking*, ginger, *Zingiber officinale* Rosc.

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1. INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia, an abnormal physiological symptom caused by a continuous increase in blood glucose levels. The increasing incidence of diabetes has become a significant public health concern worldwide. Rapid economic development, which has led to urbanization and the adoption of modern living patterns, correlates with an increase in the prevalence of diabetes in most countries worldwide. According to IDF data, an estimated 537 million people aged 20–79 years are living with diabetes. This represents 10.5% of the global population of this age group. The population is projected to increase to 643 million (11.3%) by 2030 and 783 million (12.2%) by 2045 (International Diabetes Federation, 2021)

Hyperglycemia, the leading cause of diabetic complications, arises from abnormalities in insulin secretion, insulin action, or both and chronically and heterogeneously presents as glucose, lipid, and protein metabolic dysfunction. Based on its etiology and pathogenesis, diabetes can be divided into four types: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and diabetes-induced or related to certain diseases, pathologies, and syndromes. T1DM is also known as

insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes. It is an autoimmune disease characterized by T cell-mediated destruction of pancreatic β-cells, leading to insulin insufficiency and, ultimately, hyperglycemia. T2DM is known as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, accounting for approximately 90-95% of all cases of diabetes. (Banday, Sameer and Nissar, 2020; International Diabetes Federation, 2021).

Several pharmacological strategies have been used to manage hyperglycemia in patients with diabetes. Patients with type I diabetes are frequently treated with insulin injections, whereas those with type 2 diabetes are treated with oral medicines and lifestyle modifications. Major classes of oral antidiabetic medications include biguanides, sulfonylureas, meglitinide, thiazolidinedione (TZD), dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose cotransporter (SGLT2) inhibitors, and α-glucosidase inhibitors (Chaudhury *et al.*, 2017).

Zingiber officinale Roscoe, also known as cultivated ginger, can thrive under various environmental conditions. It has been grown in India and China for many generations. Spaniards introduced this plant to the West Indies and Mexico, and obtained it from India, Southeast Asia, and China. Over time, ginger has spread to various regions, including Africa, Fiji Islands, and Australia (Govindarajan and Connell, 1983; Kumar Poudel *et al.*, 2022).

A previous study on the antidiabetic activity of juice and aqueous extract of *Z. officinale* Roscoe in streptozotocin-induced type I diabetic rats indicated that this plant could reduce total blood sugar and increase the insulin response in diabetic rats (Akhani, Vishwakarma and Goyal, 2004; Al-Amin *et al.*, 2006). *In vitro* evaluation of the antidiabetic effects on protein glycation and the diffusion of glucose in *Z. officinale* Roscoe reported that the aqueous extract has dose-dependent antidiabetic effects (Sattar *et al.*, 2012).

The chemicals in ginger responsible for their potential anti-diabetic effects have been investigated. Gingerols, the major pungent compounds in ginger, are believed to be the primary active components. Research has shown that (S)-6- and (S)-8-gingerol significantly enhance glucose uptake in cultured rat skeletal muscle cells (L6) (Li *et al.*, 2012). An *in vitro* experiment showed that 6-shogaol and 6-gingerol prevented the progression of diabetic complications and inhibited the production of AGEs by trapping methylglyoxal (MGO), the precursor of AGEs (Zhu *et al.*, 2015). It is known that the chemical components found in ginger include, quercetine, catechine, humulene, β-sesquiphellandrene, camphene, farnesene, β-sitosterol, stigmasterol, curcumin, 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, 8-shogaol, 10-shogaol, 6-paradol, 8-paradol, 10-paradol, methyl-6-gingerol dan methyl-8-gingerol (Gupta *et al.*, 2016; Munda *et al.*, 2018; Syafitri *et al.*, 2018; Zhang *et al.*, 2021).

Recently, researchers have found that unique compounds that inhibit α-glucosidase can be a highly effective way to manage high blood sugar levels after eating, especially in type 2 diabetes. These inhibitors slow down carbohydrate digestion, which delays glucose absorption in the small intestine and helps control high blood sugar levels after meals (Hossain *et al.*, 2020). Therefore, in this study, we conducted an *in silico* analysis of the molecular binding of the chemical components of ginger to α-glucosidase receptors. This study aimed to provide information on the chemical components of ginger that have potential and good conformation *in silico* anti-diabetic activity against the α-glucosidase receptor.

2. METHODS

Molecular Docking was conducted in five stages: preparation of α-glucosidase, preparation of native and test ligands, Lipinski analysis, molecular docking using Autodock Vina, and analysis and visualization of docking results.

2.1 The Preparation of α-Glucosidase

The 3D Crystal Structure of (PDB ID: 2QMJ) was retrieved from the Protein Data Bank (https://www.rcsb.org/) and saved in the PDB format. The crystal structure of α-glucosidase was selected as 2QMJ because of its association with Homo sapiens and its high resolution of 1.9 Å. The α-glucosidase complex was separated from the solvent (H_2O) and the ligands. Optimization is conducted by adding hydrogen and computing charges using Gasteiger in the AutoDock Tools software and then saved in PDBQT format.

2.2 Preparation of Native Ligands and Test Ligands

The native ligand (acarbose) was used as a reference, and the test ligands consisted of chemical components from ginger rhizomes (*Zingiber officinale Rosc*.) obtained from PubChem using the website (https://pubchem.ncbi.nlm.nih.gov/) in the SDF format. The MarvinSketch 20.19 software was utilized to convert the data into PDB format. Subsequently, the ligands were optimized using AutoDock Tools, with the Torsion Tree set to 'choose torsion' and the number of active torsions defined. Finally, they were saved in the PDBQT format.

2.3 Analysis of Lipinski

In order to ensure that the ligands possess characteristics conducive to effective oral administration based on Lipinski's guidelines, Lipinski's analysis was conducted on the SCFBio (http://scfbio-itd.res.in/software/drugdesign/lipinski.jsp#anchortag)

2.4 Molecular Docking Process

Before the docking simulation, the ligand's active site (grid box) was determined using AutoDock Tools software and saved in a (grid.txt) format. In the docking process, the receptors and ligands were saved in (*. pdbqt) format were copied into a file used to run AutoDock Vina through the command prompt (CMD).

2.5 Analysis and Visualization of Docking Results

The analysis used the binding energy parameters, root mean square deviation (RMSD) with PyMOL software, and interactions between α-glucosidase and ligands. Docking visualization was performed using the Biovia Discovery Studio Visualizer 2019 software.

3. RESULT AND DISCUSSION

Initially, the structures of the chemical components of ginger were subjected to physicochemical analysis to validate their suitability as potential drug candidates following Lipinski's rule of five. According to Lipinski's criteria, a compound qualifies as a drug candidate if it meets the following specifications: a molecular weight (MW) of ≤ 500 daltons, a maximum of 10 hydrogen acceptors (HA), no more than 5 hydrogen donors (HD), and lipophilicity (LogP) not exceeding 5 (Lipinski, 2004). The Lipinski analysis results revealed that 13 of 20 chemical compounds from ginger met all five Lipinski rule criteria, as shown in Table 1.

Before conducting docking simulations, the determination of the active site of the ligand was performed using AutoDock Tools software on a grid that was inputted with the α-glucosidase and ligand. The grid box settings obtained in this study are as follows: center_x = -20.209,

Table 1. The Results of Lipinski Analysis

No.	Ligan	Mass	HD	HA	Log P	Molar refractivity
		<500	<5	<10	<5	40-130
1	Acarbose (Pubchem)	**645**	**14**	**19**	-8.56	**137.73**
	Acarbose (Native ligand)	282	-2.24	8	0	61.63
2	Quercetine	302	5	7	2.01	74.05
3	Catechine	290	5	6	1.54	72.62
4	Humulene	204	0	0	**5.03**	68.90
5	β-Sesquiphellandrene	180	0	0	1.64	50.85
6	Camphene	136	0	0	2.99	43.75
7	Farnesene	204	0	0	**5.20**	70.99
8	β-sitosterol	414	1	1	**8.02**	128.21
9	Stigmasterol	412	1	1	**7.8**	128.12
10	Curcumin	368	2	6	3.36	102.01
11	6-Gingerol	294	2	4	3.23	82.75
12	8-Gingerol	322	2	4	4.01	91.98
13	10-Gingerol	350	2	4	4.79	101.22
14	6-Shogaol	276	1	3	4.03	81.26
15	8 Shogaol	304	1	3	4.81	90.50
16	10-Shogaol	332	1	3	**5.59**	99.73
17	6-Paradol	278	1	3	4.26	81.36
18	8-Paradol	306	1	3	**5.04**	90.59
19	10-Paradol	334	1	3	**5.82**	99.83
20	Methyl-6-Gingerol	308	1	4	3.53	87.63
21	Methyl-8-Gingerol	336	1	4	4.31	96.87

center_y = -6.763, center_zs = 9.393, size_x = 12, size_y = 10, size_z = 12, and spacing (angstrom) = 1.

The docking result analysis in this study included the values of ΔG_{bind} (binding energy), RMSD (root mean square deviation), and the interaction between α-glucosidase and the ligands. The ΔG_{bind} values (binding energies) were examined based on the conformations of each test ligand and the native ligand obtained from docking and sorted from the smallest to the largest values. The data for ΔG_{bind} values of ligands against the α-glucosidase in Table 2 indicate binding energy values within the range of -7.3 kcal/mol to -4.0 kcal/mol. For the native ligand (acarbose), the binding energy was -6.9 kcal/mol. Among the test ligands, four compounds have lower binding energy values compared to acarbose: quercetin (-7.3 kcal/mol), catechin (-7.1 kcal/mol), curcumin (-7.0 kcal/mol), and 6-gingerol (-7.0 kcal/mol). Small ΔG_{bind} values indicated the formation of stable conformations with high affinity, resulting in more effective pharmacological effects. In contrast, high ΔG_{bind} values indicate less stable complexes with lower affinities (Rachmania, Supandi and Anggun Larasati, 2015; Adelina, 2020). Other compounds that have the binding energy value close to acarbose include β-sesquiphellandrene (-6.4 kcal/mol), farnesene (-6.1 kcal/mol), 8-gingerol (-6.2 kcal/mol), 10-gingerol (-6.2 kcal/mol), 6-shogaol (-6.5 kcal/mol), 8-shogaol (-6.3 kcal/mol), 10-shogaol (-6.2 kcal/mol), 6-paradol (-6.3 kcal/mol), 8-paradol (-6.1 kcal/mol), 10-paradol (-6.2 kcal/mol), methyl-6-gingerol (-6.5 kcal/mol), methyl-8-gingerol (-6.5 kcal/mol).

Table 2. Interaction results of α-glucosidase with ligands

No.	Ligand	ΔG_{bind} (kkal/mol)	Category	Chemical Bonding	Amino Acid Residues and Bond Distances
1.	Acarbose (Native ligand)	-6.9	Hydrogen Bonding	*Conventional Hydrogen Bond*	Asp 327 (2.63); His 600 (2.19); Asp 542 (2.88); Arg 526 (2.17); Asp 203 (3.23)
				Pi-Donor Hydrogen Bond	Trp 406 (3.94)
			Hydrophobic	*Pi-Alkyl*	Phe 575 (4.87); Tyr 299 (4.52); Trp 406 (5.46)
2.	*Quercetine*	-7.3*	Hydrogen Bonding	*Conventional Hydrogen Bond*	Asp 203 (2.03); Asp 542 (2.40); Asp 327 (2.25)
			Hydrophobic	*Pi-Pi Stacked*	Phe 575 (5.01)
				Pi-Pi T-shaped	Trp 406 (4.84)
			Electrostatic	*Pi-Anion*	Asp 443 (4.23); Asp 542 (4.58)
			Unfavorable	*Unfavorable Donor-Donor*	Ser 448 (2.30); His 600 (1.98)
3.	*Catechine*	-7.1*	Hydrogen Bonding	*Conventional Hydrogen Bond*	Asp 327(2.44)
			Hydrophobic	*Pi-Pi Stacked*	Phe 575 (5.08)
				Pi-Pi T-shaped	Trp 406 (5.69)
			Electrostatic	*Pi-Anion*	Asp 443 (4.14)
4.	*Humulene*	-5.7	Hydrophobic	*Alkyl*	Met 444 (4.85)
				Pi-Alkyl	Phe 575 (4.34); Phe 450 (4.97); Trp 406 (4.92)
5.	*β-Sesquiphellandrene*	-6.4	Hydrophobic	*Alkyl*	Ala 576 (3.69); Ile 346 (5.32)
				Pi-Alkyl	Phe 575 (4.99); Tyr 299 (4.59); His 600 (5.16); Trp 441 (4.59)
6.	*Camphene*	-5.5	Hydrophobic	*Alkyl*	Met 444 (4.64); Ile 328 (4.24); Ile 364 (5.49)
				Pi-Alkyl	His 600 (5.44); Phe 575 (5.14); Trp 441 (4.99); Trp 539 (5.49); Trp 406 (4.50); Tyr 299 (4.07)
7.	*Farnesene*	-6.1	Hydrophobic	*Pi-sigma*	Typ 299 (3.67)
				Alkyl	Ile 328 (4.31); Met 444 (5.13)
				Pi-Alkyl	His 600 (4.99); Phe 450 (4.32); Phe 575 (4.95); Trp 441 (4.71); Trp 406 (4.52)
8.	*β-sitosterol*	-4.8	Hydrophobic	*Pi-sigma*	Phe 450 (3.71)
				Alkyl	Lys 480 (4.50)
				Pi-Alkyl	Phe 575 (5.14); Trp 406 (4.92); Tyr 299 (4.93)
			Unfavorable	*Unfavorable Donor-Donor*	Asp 327 (2.14)
9.	*Stigmasterol*	-4.0	Hydrophobic	*Pi-sigma*	Tyr 299 (3.88)
				Alkyl	Ala 576 (3.71); Met 444 (5.27)
				Pi-Alkyl	Phe 575 (4.99); Trp 406 (4.71); Tyr 605 (4.92)
			Unfavorable	*Unfavorable Donor-Donor*	Asp 443 (2.22)
10.	*Curcumin*	-7.0*	Hydrogen Bonding	*Conventional Hydrogen Bond*	Arg 526 (2.48); Asp 203 (2.15); Asp 327 (3.42); Asp 443 (3.49)
			Hydrophobic	*Alkyl*	Ile 364 (5.34)
				Pi-Alkyl	Phe 450 (5.24); Trp 441 (5.22)
				Pi-Pi T-shaped	Trp 406 (5.38)
			Electrostatic	*Pi-Anion*	Asp 542 (3.84)

*Values of ΔG_{bind} compounds are lower than acarbose.

Table 2 Continue

No.	Ligand	ΔG_{bind} (kkal/mol)	Category	Chemical Bonding	Amino Acid Residues and Bond Distances
11.	*6-Gingerol*	-7.0*	Hydrogen Bonding	*Conventional Hydrogen Bond*	Arg 526 (2.29); Tyr 605 (1.98)
			Hydrophobic	*Alkyl*	Ile 328 (4.04)
				Pi-Alkyl	Trp 406 (4.43); Tyr 299 (3.67)
				Pi-Pi T-shaped	Phe 575 (4.81)
12.	*8-Gingerol*	-6.2	Hydrogen Bonding	*Conventional Hydrogen Bond*	Arg 526 (2.11); Asp 203 (2.22); Asp 327(1.91); Asp 542 (3.36)
			Hydrophobic	*Pi-Alkyl*	His 600 (4.34); Phe 575 (4.69); Trp 441 (5.04); Trp 539 (4.62); Tyr 299 (4.92)
			Electrostatic	*Pi-Anion*	Asp 443 (4.20)
13.	*10-Gingerol*	-6.2	Hydrogen Bonding	*Conventional Hydrogen Bond*	Asp 542 (2.68)
			Hydrophobic	*Pi-Alkyl*	Ala 576 (4.44); His 600 (4.77); Phe 575 (4.57); Trp 406 (5.02); Trp 441 (5.34); Tyr 299 (5.07)
			Unfavorable	*Unfavorable Donor-Donor*	Arg 526 (1.35)
14.	*6-Shogaol*	-6.5	Hydrogen Bonding	*Conventional Hydrogen Bond*	Asp 327 (2.64)
			Hydrophobic	*Alkyl*	Ala 576 (4.60)
				Pi-Alkyl	His 600 (4.40); Phe 575 (4.50); Trp 441 (5.22); Trp 539 (4.86); Tyr 605 (5.00)
15.	*8-Shogaol*	-6.3	Hydrogen Bonding	*Conventional Hydrogen Bond*	Asp 327 (2.74); Asp 443 (3.07)
			Hydrophobic	*Alkyl*	Ala 576 (4.86)
				Pi-Alkyl	His 600 (4.39); Phe 575 (4.58); Trp 441 (5.13); Trp 539 (4.89); Tyr 299 (5.09)
16.	*10-Shogaol*	-6.2	Hydrogen Bonding	*Conventional Hydrogen Bond*	Arg 526 (2.04); Asp 443 (2.82)
			Hydrophobic	*Pi-Alkyl*	His 600 (4.39); Phe 450 (4.64); Phe 575 (4.36); Trp 406 (5.04); Trp 441 (5.34); Trp 539 (4.98); Tyr 299 (5.07)
			Electrostatic	*Pi-Anion*	Asp 443 (4.19)
17.	*6-Paradol*	-6.3	Hydrogen Bonding	*Conventional Hydrogen Bond*	Arg 526 (2.18)
			Hydrophobic	*Alkyl*	Ala 576 (3.83); Ile 328 (4.12)
				Pi-Alkyl	Trp 406 (4.38); Tyr 299 (3.75)
				Pi-Pi T-shaped	Phe 575 (4.82)
18.	*8-Paradol*	-6.1	Hydrogen Bonding	*Conventional Hydrogen Bond*	Arg 526 (2.18); Asp 327 (2.44)
				Carbon Hydrogen Bond	Asp 542 (3.30)
			Hydrophobic	*Pi-Alkyl*	His 600 (4.38); Phe 575 (4.69); Trp 441 (5.12); Trp 539 (4.76); Tyr 605 (5.17)

*Values of ΔG_{bind} compounds lower than acarbose.

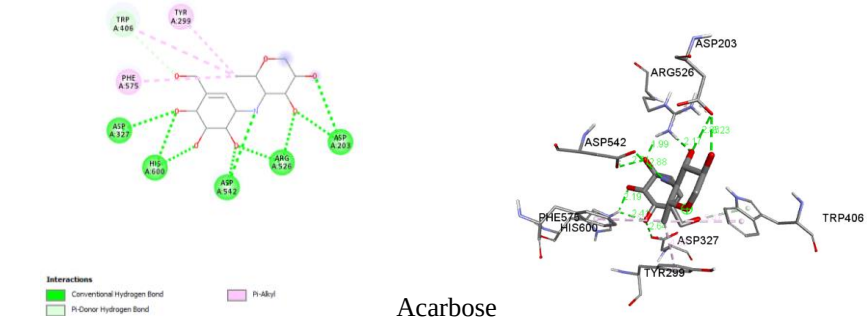
Table 2. Continue

No.	Ligand	ΔG_{bind} (kkal/mol)	Category	Chemical Bonding	Amino Acid Residues and Bond Distances
19.	*10-Paradol*	-6.2	Hydrogen Bonding	*Carbon Hydrogen Bond*	Asp 542 (3.26)
			Hydrophobic	*Alkyl*	Ala 576 (3.77)
				Pi-Alkyl	His 600 (4.43); Phe 575 (4.92); Trp 441 (5.15); Trp 539 (4.73); Tyr 299 (4.78)
			Electrostatic	*Pi-Anion*	Asp 443 (4.19)
20.	*Methyl-6-Gingerol*	-6.5	Hydrogen Bonding	*Conventional Hydrogen Bond*	Arg 526 (2.73); Asp 443 (2.31); Thr 205 (2.66)
				Carbon Hydrogen Bond	Asp 203 (3.50); Asp 542 (3.30)
			Hydrophobic	*Alkyl*	Ala 576 (3.71); Ile 328 (4.33)
				Pi-Alkyl	Tyr 299 (3.85); Trp 406 (4.33)
			Electrostatic	*Pi-Anion*	Asp 542 (3.70)
21.	*Methyl-8-Gingerol*	-6.3	Hydrogen Bonding	*Conventional Hydrogen Bond*	Asp 203 (2.17)
			Hydrophobic	*Alkyl*	Ile 328 (4.15)
				Pi-Alkyl	Phe 575 (5.07); Trp 406 (5.49); Tyr 299 (3.71); Tyr 605 (5.32)

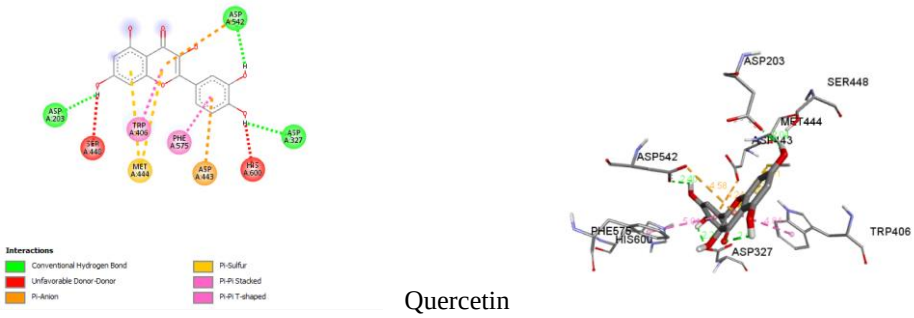
The RMSD value obtained in this study for the docking of the native ligand (acarbose) with α-glucosidase was 0.384 Å. This result suggests that the docking method employed is valid and suitable for docking test ligands from ginger rhizomes. The interactions between the macromolecule (α-glucosidase) and the test ligands, as well as the native ligand (acarbose), were analyzed using Biovia Discovery Studio software. These interactions encompassed hydrogen bonds, hydrophobic, electrostatic, and unfavorable interactions, as detailed in Table 2.

Molecular docking results indicated that the native ligand acarbose is bonded to α-glucosidase through a variable bond with amino acid residues Asp 327, His 600, Asp 542, Arg 526, Asp 203, Trp 406, Phe 575, and Tyr 299. A previous study indicated that acarbose was bonded to α-glucosidase through the amino acid residues Arg 202, Glu 404, Val 405, and Trp 406 (Rachmania, Supandi and Anggun Larasati, 2015), Tyr 299, Phe 575, Trp 406, Met 444, His 600 (Dwitiyanti *et al.*, 2018), or 1,2-benzothiazine derivatives His 600, Asp 542, Arg 526, Asp 327, Met 444, and Lys 480 (Saddique *et al.*, 2021).

Molecular docking results indicated that test ligands with lower and closer binding energies to acarbose, such as quercetin, catechin, curcumin, 8-gingerol, 6-shogaol, 8-shogaol, and 8-paradol, bind to α-glucosidase through hydrogen bonding with the Asp 327 amino acid residue. Test ligands, such as quercetin, curcumin, 8-gingerol, methyl-6-gingerol, and methyl-8-gingerol, form hydrogen bonds with the Asp 203 residue. In the test ligands curcumin, 6-gingerol, 8-gingerol, 10-shogaol, 6-paradol, 8-paradol, and methyl-6-gingerol, hydrogen bonding occurs with residue Arg 526. In quercetin, 8-gingerol, 10-gingerol, 8-paradol, 10-paradol, and methyl-6-gingerol, hydrogen bonding was observed with Asp 542. Visualization of the interactions between quercetin, catechin, curcumin, and 6-gingerol and the amino acid residues of α-glucosidase is shown in Figure 1.



Acarbose



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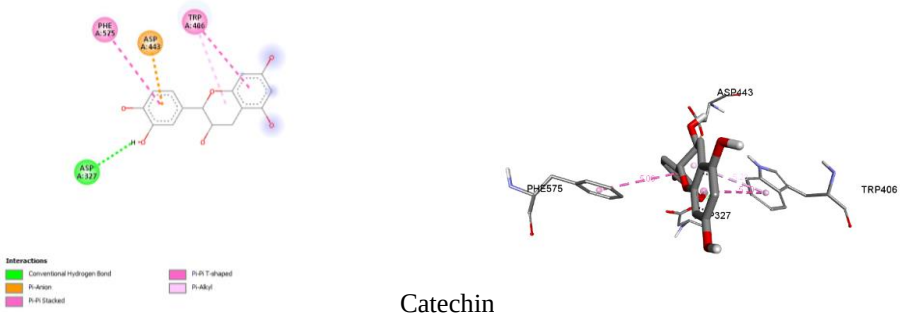
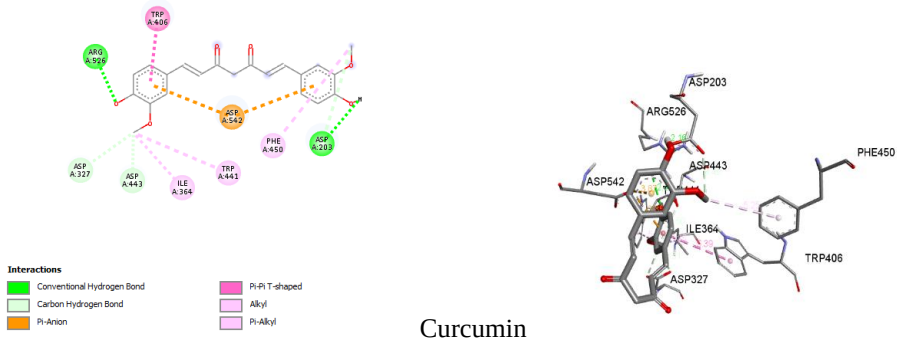
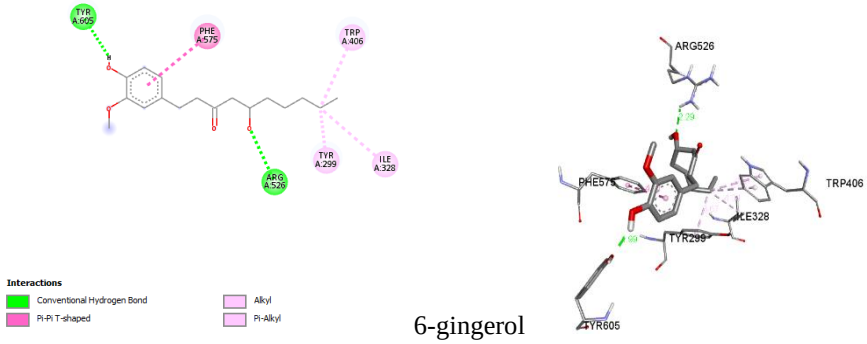


Catechin



Curcumin



6-gingerol

Figure 1. Molecular docking of protein (PDB ID: 2QMJ) - ligands. The amino acid residues show the specific interaction to ligand

An increased number of hydrogen bonds enhances the stability of ligand-receptor binding because the structural stability of a protein is influenced by hydrogen bonds (Sumilat, Pangkey and Luntungan, 2021; Rena, Nurhidayah and Rustan, 2022). More hydrogen bonds result in lower binding energy values (Kurnyawaty, Suwito and Kusumattaqiin, 2021). However, the presence of multiple hydrogen bonds does not guarantee excellent stability. Among ligands forming more than one hydrogen bond, only quercetin (-7.3 kcal/mol), curcumin (-7.0 kcal/mol), and 6-gingerol (-7.0 kcal/mol) exhibit ΔG_{bind} (binding energy) values approaching that of acarbose (-6.9 kcal/mol). Ligands forming a single hydrogen bond with ΔG_{bind} values close to that of acarbose include catechin (-7.1 kcal/mol). Ligands that formed hydrogen bonds with Asp 327, Asp 203, Arg 526, and Asp 542, such as quercetin, catechin, curcumin, and 6-gingerol, showed the best ΔG_{bind} values among the tested and reference compounds, indicating their strong binding affinity, potentially due to hydrogen bonding similar to acarbose at Asp 327, Asp 203, Arg 526, and Asp 542.

The larger the bond distance, the easier it is to break. Conversely, if the bond distance is shorter, the bond is stronger (Rachmania, Supandi and Anggun Larasati, 2015). In this study, the bond distances between amino acid residues and ligands in α-glucosidase range from 1.35 to 5.58 Å. The ginger test ligands and native ligand (acarbose) exhibited different bond distances. Based on the donor-acceptor distances, 2.2-2.5 Å indicates strong interactions, 2.5-3.2 Å indicates moderate interactions, and 3.2-4.0 Å indicates weak interactions (Hanif, Lukis and Fadlan, 2020).

Previous *in vitro* studies have shown that quercetin, catechin, curcumin and 6-gingerol actively inhibit α-glucosidase at the IC_{50} values are 65.52 µg/mL (Limanto *et al.*, 2019), 30.85 µg/mL (Arundita *et al.*, 2020), 6. 9 µg/mL (Lekshmi *et al.*, 2014) and 21.55 µg/mL (Mohammed *et al.*, 2017). Based on these findings, it can be predicted that these chemical components are responsible for the anti-diabetic activity of ginger. Furthermore, the presence of compounds such as β-sesquiphellandrene, farnesene, 8-gingerol, 10-gingerol, 6-shogaol, 8-shogaol, 10-shogaol, 6-paradol, 8-paradol, 10-paradol, methyl-6-Gingerol, and methyl-8-gingerol further enhances the anti-diabetic potential of ginger rhizomes.

4. CONCLUSION

The docking analysis reveals that four compounds from ginger components have lower binding energy values compared to acarbose, namely quercetin (-7.3 kcal/mol), catechin (-7.1 kcal/mol), curcumin (-7.0 kcal/mol), and 6-gingerol (-7.0 kcal/mol), while acarbose, as the native ligand, demonstrates a ΔGbind value of -6.9 kcal/mol. The interaction of the test ligands with α-glucosidase involves hydrogen bonding, hydrophobic interactions, electrostatic forces, and unfavorable interactions.

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