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Molecular Docking of Active Compound of Okra (*Abelmoschus esculentus* L.) on *α*-Glucosidase as Antidibetic Mellitus Drug Candidate

Penambatan Molekuler Senyawa Aktif Okra (*Abelmoschus esculentus* L.) Pada Enzim *α*-Glukosidase Sebagai Kandidat Obat Antidiabetes Melitus

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ABSTRACT

Diabetes mellitus (DM) is a leading cause of death among degenerative diseases, primarily due to impaired insulin function that disrupts carbohydrate metabolism. One therapeutic strategy involves α-glucosidase inhibitors that delay glucose absorption. *Abelmoschus esculentus* (okra) is rich in phenolic and flavonoid compounds with antihyperglycemic and antioxidant activity, suggesting potential as α-glucosidase inhibitors. This study evaluated the inhibitory potential of okra-derived compounds against α-glucosidase using in silico molecular docking with PLANTS and YASARA Structure. The analysis included physicochemical screening, ligand–receptor preparation, and docking simulations, assessing docking score, Gibbs free energy (ΔG), and dissociation constant (Kd). Cannabiscitrin, a flavonoid from okra, demonstrated the strongest binding affinity, outperforming the reference drug acarbose in all parameters. These findings suggest its potential as an alternative antidiabetic agent.

ABSTRAK

Diabetes melitus (DM) merupakan penyebab kematian tertinggi ketiga dari penyakit degeneratif, terutama akibat gangguan fungsi insulin yang memengaruhi metabolisme karbohidrat. Salah satu strategi terapi adalah penggunaan inhibitor α-glukosidase yang menghambat penyerapan glukosa. *Abelmoschus esculentus* (okra) mengandung senyawa fenolik dan flavonoid dengan aktivitas antihiperglikemik dan antioksidan yang kuat, sehingga berpotensi sebagai inhibitor α-glukosidase alami. Penelitian ini mengevaluasi potensi inhibitor senyawa aktif okra terhadap α-glukosidase secara in silico menggunakan program PLANTS dan YASARA Structure. Analisis mencakup prediksi sifat fisikokimia, preparasi ligan dan reseptor, serta simulasi penambatan molekul berdasarkan skor docking, energi bebas Gibbs (ΔG), dan konstanta disosiasi (Kd). Hasil menunjukkan bahwa cannabiscitrin, senyawa flavonoid dari okra, memiliki afinitas ikatan paling kuat, melampaui obat acarbose dalam semua parameter. Temuan ini menunjukkan potensi cannabiscitrin sebagai kandidat alternatif obat antidiabetes.

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1. INTRODUCTION

The development of social status, economic conditions, and lifestyle within communities has led to a shift in disease patterns and causes of mortality, marked by a decline in infectious diseases and a rise in degenerative diseases, including diabetes mellitus (DM). According to the International Diabetes Federation (IDF), approximately 1 in 11 adults (415 million people) aged 20–79 years were diagnosed with DM in 2015. This number was projected to increase to 642 million by 2040 if effective interventions were not implemented (Siddique et al., 2022). Globally, the prevalence of DM rose from 2,608 cases per 100,000 people in 1990 to 6,661 per 100,000 in 2021, more than doubling over three decades. Similarly, the mortality rate increased from 12.60 per 100,000 in 1990 to 20.99 per 100,000 in 2021 (Institute for Health Metrics and Evaluation, 2021). In Indonesia, the prevalence of DM among adults steadily increased from 5.7% in 2007 to 6.9% in 2013 and further to 8.5% in 2018 (Ministry of Health Republic of Indonesia, 2007, 2013, 2018). Moreover, a significant number of individuals remained undiagnosed due to the asymptomatic nature of DM in its early stages. This lack of early detection contributed to disease progression and the development of complications, emphasizing the need for better prevention and screening measures (Fen, 2017).

Diabetes mellitus is a metabolic disorder characterized by insufficient insulin secretion by pancreatic β-cells, increased insulin resistance, or impaired insulin action in target tissues. DM is classified into type 1 and type 2. Type 1 DM results from absolute insulin deficiency due to pancreatic β-cell destruction, which prevents insulin production. It is primarily believed to be an autoimmune disorder, potentially triggered by infections or environmental factors (Popoviciu et al., 2023). Conversely, type 2 DM is characterized by insulin resistance, where insulin receptors become insensitive to insulin signalling (Antar et al., 2023). This dysfunction leads to postprandial hyperglycemia (PPHG), defined as plasma glucose levels of ≥200 mg/dL approximately 1.5–2 hours after a meal, compared to <140 mg/dL in non-diabetic individuals. Prolonged hyperglycemia has been associated with macrovascular and microvascular complications, including cardiovascular disease, neuropathy, stroke, kidney failure, and other conditions (Maffettone et al., 2018; Zakir et al., 2023). Thus, controlling PPHG is a key strategy in managing type 2 DM.

One approach to regulating PPHG in type 2 DM involves inhibiting carbohydrate-hydrolyzing enzymes, particularly α-glucosidase. This enzyme catalyzes the hydrolysis of unabsorbed oligosaccharides and disaccharides into monosaccharides, which are absorbed in the jejunum and enter systemic circulation, leading to hyperglycemia. Alpha-glucosidase inhibitors (AGIs) act as pseudo-carbohydrates, competitively inhibiting the enzyme's activity on intestinal cells. However, pharmaceutical AGIs such as acarbose and voglibose, along with other antidiabetic medications, have been associated with adverse effects, including flatulence, severe abdominal discomfort, allergic reactions, hypoglycemia, hepatotoxicity, lactic acidosis, abdominal distension, diarrhea, and pneumatosis cystoides intestinalis (Emilda, 2018; Kashtoh & Baek, 2022). Furthermore, these drugs exhibit limited efficacy, as indicated by their high IC50 values (Silva et al., 2016). Therefore, alternative treatments with greater efficacy and fewer side effects are urgently needed to enhance the safety and tolerability of antidiabetic therapies.

Traditional medicine has emerged as a promising alternative due to its relatively lower incidence of adverse effects compared to conventional pharmaceuticals. According to data from the National Workshop on Medicinal Plants, Indonesia has approximately 30,000 plant species, with 940 exhibiting medicinal properties. One such plant with potential antidiabetic effects is okra (*Abelmoschus esculentus*) (Ningsih, 2016; Megawati et al., 2020). Okra is recognized for its ability to lower blood glucose levels and improve glucose metabolism by delaying intestinal glucose absorption, thereby maintaining glycemic stability (Gomes et al., 2023; Bahari et al., 2024). Additionally, the fruit, pod, and seed of okra are rich in phenolic and flavonoid content that exhibit antihyperglycemic, antihyperlipidemic, and potent antioxidant activities with α-glucosidase inhibitory activity (Liao et al., 2012; Sabitha et al., 2012; Abdel-Razek et al., 2023).

In silico approaches such as molecular docking represent valuable tools in modern drug discovery and development. This method allows prediction of the stability and interaction between ligands and target proteins. In this study, molecular docking was conducted using two programs: YASARA and the Protein-Ligand ANT System (PLANTS). These programs employ different algorithms, resulting in different analytical parameters. YASARA assesses binding free energy (ΔG), dissociation constant (Kd), and interaction types, while PLANTS computes docking scores related to ligand poses and the relationship between chemical structure and biological activity as an antidiabetic agent. The combined use of these two programs aims to strengthen the findings in identifying okra as a potential antidiabetic drug candidate.

2. METHODS

2.1. Physicochemical Prediction of Ligands

The physicochemical prediction was conducted as an initial virtual screening step, following the methodology described by Rajalakshmi et al., (2021). Twenty-seven test ligands derived from okra (*Abelmoschus esculentus*) and one reference ligand, acarbose, were obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) (**Table 1**). Physicochemical properties were assessed based on Lipinski's Rule of Five, considering parameters such as molecular weight, hydrogen bond donors and acceptors, Log P, and molar refractivity.

2.2. Preparation of Protein Target

The *α*-glucosidase protein structure (PDB ID: 2QMJ) was downloaded from the RCSB Protein Data Bank (www.rcsb.org/pdb) in PDB format. The protein was then

prepared by removing any water molecules and bound ligands, and adding hydrogen ions using YASARA structure (Krieger, Vienna, Austria). The results were saved in PDB file format (*.pdb) and protein.mol2 file format.

Table 1. Phenolic and Flavonoid Compounds Identified in *Abelmoschus esculentus* (Okra)

No	Ligands	Part Used
	Phenolic acid	
PO1	Oxalic acid	Pods
PO2	Fumaric acid	Pods
PO3	Malic acid	Pods
PO4	p-Methoxy benzoic acid	Flower and fruit
PO5	Vanilic acid	Pods
PO6	Shikimic acid (Shikimate)	Pods
PO7	Citric acid	Pods
	Flavonoids	
FO1	Myricetin	Flowers
FO2	Kaempferol-3-O-glucoside (Syn.:astragalin)	Flowers
FO3	Cannabiscitrin	Flowers
FO4	Rutin (Syn.: quercetin3-rutinoside)	Flowers
FO5	FloramanosideD	Flowers
FO6	Quercetin diglucoside	Flowers
FO7	isoquercetin	Flowers
FO8	Hyperin (Syn.: hyperoside or quercetin 3-galactoside)	Flowers and fruits
FO9	Quercetin-3-gentiobioside	Pods
FO10	quercetin-3-sambubioside	Pods
FO11	Quercetin-O-pentosyl-7-O-hexoside	Pods
FO12	Isorhamnetin 3-O-glucoside-7-O-xyloside	Pods
FO13	Epicatechin	Fruits
FO14	Gallocatechin	Fruits
FO15	Procyanidin B1 (Syn.: endotelon)	Fruits
FO16	Procyanidin B2 (Syn.: procyanidol B2)	Fruits
FO17	Cyanidin 3-glucoside (Syn.: kuromanin or idein)	Pods
FO18	Cyanidin 4′-glucoside	Pods
FO19	Cyanidin 3-sambubioside (Syn.: sambicyanin)	Pods
FO20	Delphinidin 3-O-sambubioside	Pods

2.3. Preparation of Co-crystal and Test Ligands Using PLANTS

Ligands (both co-crystal and test compounds) were prepared by MarvinSketch (Certara, United States). Protonation states were optimized at physiological pH (7.4) using the Major Microspecies method. Conformers were generated, and the most favorable conformation for binding to the α-glucosidase protein was selected. By varying the number of conformations, docking scores reflecting the best ligand poses in the protein's binding pocket were obtained using the PLANTS docking program (Korb et al., 2009).

2.4. Preparation of Native and Test Ligands Using YASARA Structure

The three-dimensional (3D) structure of the target protein was obtained in .pdb format and opened with YASARA. The co-crystallized ligand was separated from the protein and saved in a new PDB file (.pdb). Reference ligand and test ligands were retrieved in 3D *.sdf format from PubChem. Furthermore, both ligands were subjected to energy minimization in YASARA before being stored in PDB format (.pdb).

2.5. Validation of Molecular Docking Protocols

Docking validation for both YASARA and PLANTS was conducted using Root Mean Square Deviation (RMSD) analysis using YASARA structure. The docking protocol was considered valid when RMSD value $\leq$ 2.5 Å, which is indicated higher similarity between predicted and experimental ligand positions.

2.6. Molecular Docking Simulation

For PLANTS, docking was executed in the Windows command line using validated binding site parameters. The ligand conformations that produced the most negative binding affinity scores were selected for subsequent analysis and visualization.

In YASARA, docking was performed on the prepared protein (*.pdb) using the validated grid box parameters, with the results saved in *.sce format. The analyzed parameters were consistent with those used during the validation stage.

2.7. Visualization of Protein–Ligand Interactions

The docking results from PLANTS in mol2 format and YASARA in yob format were converted into *.pdb using YASARA structure. The protein and ligand from PLANTS, attached to receptors using

Discovery Studio Client 2016 (Pilot, 2016). Protein–ligand interactions were then visualized in two dimensions using LigPlot+ v1.5.4 (Laskowski et al., 2011) respectively, with an interaction radius set to 5 Å from the docked ligand site.

3. RESULTS AND DISCUSSION

3.1. Analysis of Physicochemical Properties of Ligands

The prediction of physicochemical properties of a compound intended for development as a drug is a critical step in drug discovery. The physicochemical analysis of ligands was conducted using Lipinski's Rule of Five, a useful tool for predicting a compound's "druggability" or oral bioavailability (Nhlapho et al., 2024). A compound is considered to possess good permeability and absorption if it has a molecular weight under 500 Da, fewer than five hydrogen bond donors, fewer than ten hydrogen bond acceptors, a Log P value below 5, and a molar refractivity between 30–140 (Lipinski et al., 2001). Compounds with molecular weights above 500 Da were generally less able to permeate cell membranes (Syahputra et al., 2014). The hydrogen bonding parameters reflect the energy required for the absorption of a compound; a higher number of hydrogen bond donors and acceptors increases hydrogen bonding potential, which makes absorption more difficult. Log P indicates the compound's lipophilicity (Widyasari et al., 2019), while lower molar refractivity values were associated with better absorption (Chedik et al., 2017). A ligand was considered compliant with Lipinski's rule if it did not violate more than two of these parameters (Lipinski et al., 1997; Daina et al., 2017).

Based on the analysis, the reference ligand (acarbose) and eleven flavonoid-derived test ligands did not fully complywith Lipinski's rule, each violating two to four parameters (**Table 2**), indicating potentially limited permeability. The ligand that satisfied all criteria **was** subsequently selected for docking simulation.

3.2. Validation of Docking Method and Molecular Docking

Molecular docking is a computational technique used to predict both the binding affinity and interaction patterns between a compound and its target protein (Saputri et al., 2016). In this study, docking was performed using the α-glucosidase protein (PDB ID: 2QMJ), which consisted of 868 residues grouped into five main domains: the P-type trefoil domain, N-terminal β-sandwich domain, catalytic barrel domain, proximal C-terminal domain, and distal C-terminal domain.

Table 2. Physicocemical predictions of ligands according to Lipinski's rule

Ligands	Relative Atomic Mass (Da)	Hydrogen Bond Donor	Hydrogen Bond Acceptor	Log P	Molar Refractivity
Acarbose (Reference)	645.00	14.00	19.00	-8.22	138.73
Phenolic acid					
PO1	90.00	2.00	4.00	-0.84	15.27
PO2	116.00	2.00	4.00	-0.29	24.41
PO3	134.00	3.00	5.00	-1.09	25.90
PO4	152.00	1.00	3.00	1.34	39.95
PO5	168.00	2.00	4.00	1.10	41.62
PO6	174.00	4.00	5.00	-1.52	38.36
PO7	192.00	4.00	7.00	-1.25	37.09
Flavonoids					
FO1	318	6.00	8.00	1.72	75.72
FO2	448.00	7.00	11.0	-0.43	104.61
FO3	480.00	9.00	13.00	-0.81	108.44
FO4	610.00	10.00	16.00	-1.88	137.50
FO5	624.00	9.00	16.00	-1.58	142.38
FO6	626.00	11.00	17.00	-2.91	138.91
FO7	464.00	8.00	12.00	-0.73	106.27
FO8	464.38	8.00	12.00	-0.73	106.27
FO9	626.00	11.00	17.00	-2.91	138.91
FO10	596.00	10.00	16.00	-2.27	132.90
FO11	596.50	10.00	16.00	1.69	127.65
FO12	610.50	9.00	16.00	-2.31	137.88
FO13	290.26	5.00	6.00	1.55	72.62
FO14	306.26	6.00	7.00	1.25	74.29
FO15	578.52	10.00	12.00	2.99	143.39
FO16	594.50	10.00	12.00	2.99	143.39
FO17	450.39	8.00	11.00	0.19	106.45
FO18	450.39	8.00	11.00	0.38	107.11
FO19	581.50	10.00	15.00	-1.34	133.08
FO20	598.15	11.00	16.00	1.45	128.22

Description: yellow highlighted numbers = violating Lipinski's rule

The active site was surrounded by the N-terminal domain, protein domain 1, and protein domain 2 (**Figure 1**). It included residues Asp203, Tyr299, Asp327, Ile328, Ile364, Trp406, Trp441, Asp443, Met444, Phe450, Arg526, Asp542, and His600. The catalytic triad—Tyr299, Asp443, and Asp542—formed the core of enzymatic activity, where Tyr299 and Asp542 functioned as acid–base catalysts and Asp443 acted as the nucleophile (Sim et al., 2008).

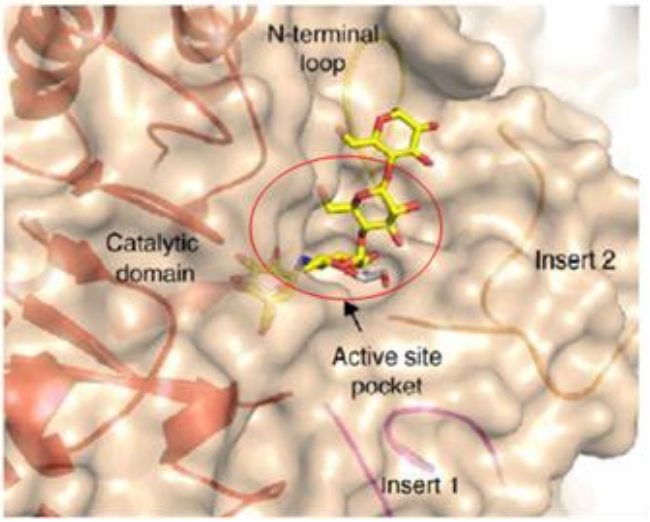


Figure 1. 3D visualization of *α*-glucosidase active site (Sim et al., 2008)

Prior to docking the test ligands, the method was validated by redocking acarbose, a known competitive inhibitor of α-glucosidase widely used as an antidiabetic agent (He, 2014). Validation involved generating a grid box around the known binding site and evaluating the Root Mean Square Deviation (RMSD) between docked and crystallographic poses. A method was deemed valid when the RMSD value was less than 2.5 Å (Rollando et al., 2018). The resulting RMSD values of 1.6321 Å and 1.1761 Å (**Appendix 1**) showed strong consistency with the native pose (**Figure 2**), thereby confirming that the docking parameters could be applied to the test ligands.

Docking simulations were performed on seven phenolic and nine flavonoid compounds derived from okra, and the results were compared to those of acarbose, the native ligand. Docking scores from PLANTS and YASARA revealed the binding affinities of these compounds for the target protein. A higher (more negative) binding energy indicated stronger ligand–receptor affinity and more stable complexes (Pratama & Suhartono, 2018). Additionally, lower ΔG values corresponded to more spontaneous reactions and were subsequently used to calculate the dissociation constant (Kd); lower ΔG resulted in a lower Kd, indicating higher binding affinity (Friedman, 2022).

Acarbose, used as a reference, exhibited a PLANTS score of –89.96 and a YASARA ΔG of –8.43 kcal/mol, yielding a Kd of 66.40 × 10^4 pM. By contrast, phenolic acids (PO1–PO7) demonstrated weaker binding across both platforms, with PLANTS scores from –43.50 to –63.43, ΔG values between –4.17 and –6.58 kcal/mol, and Kd values ranging from 10^6 to 10^7 pM (**Table 3**).

Flavonoids (FO1–FO18) exhibited significantly stronger binding, with PLANTS scores ranging from –72.40 to –96.32 and ΔG values from –7.46 to –9.12 kcal/mol. FO3, in particular, exhibited the most negative docking score (–96.32) and a ΔG of –9.12 kcal/mol, along with a Kd of 20.72 × 10^4 pM, indicating superior binding affinity over acarbose. Compounds FO2, FO7, and FO17 also exhibited favorable docking results, with values comparable to those of the reference drug (**Table 3**). Overall, these findings indicated that okra-derived phenolic acids possessed limited inhibitory potential, whereas several flavonoids demonstrated strong inhibitory effects against α-glucosidase. Among them, FO3 emerged as the most promising ligand, indicating higher binding affinity and potential activity than acarbose.

3.3. Analysis and Visualization of Molecular Docking

Further analysis and visualization were conducted on test ligands whose docking scores were more favorable (more negative) than that of the reference ligand in both PLANTS and YASARA. Two-dimensional visualization (**Figure 3**) was performed to evaluate specific protein–ligand interactions. This approach provided insight into how the reference and test compounds interacted with residues in the enzyme's active and catalytic sites, as outlined by Sim et al. (2008) (**Table 4**). The catalytic residues include Tyr299, Asp443, and Asp542, while the broader active site includes Asp203, Asp327, Ile328, Ile364, Trp406, Trp441, Met444, Phe450, Arg526, and His600.

a b

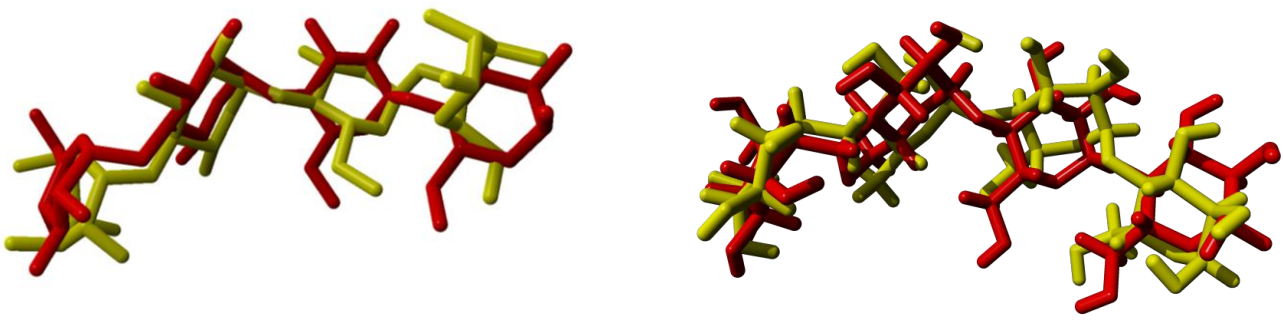


Figure 2. Acarbose Pose from Validation Results. Red is a native ligand, yellow is a redocking ligand a) PLANTS b) YASARA

Table 3. The results of molecular docking

Ligands	PLANTS	YASARA STRUCTURE	
	Score docking	ΔG (kcal/mol)	Kd (pM)
Acarbose (Reference)	-89.96	-8.43	66.40×10^{4}
Phenolic acid			
PO1	-43.50	-4.17	87.33×10^{7}
PO2	-53.96	-5.77	58.07×10^{6}
PO3	-50.26	-5.30	13.01×10^{7}
PO4	-51.93	-5.30	13.01×10^{7}
PO5	-57.46	-6.45	18.62×10^{6}
PO6	-63.43	-6.58	14.99×10^{6}
PO7	-50.88	-6.23	27.35×10^{6}
Flavonoids			
FO1	-72.40	-7.94	15.13×10^{5}
FO2	-83.25	-8.41	34.79×10^{4}
FO3	-92.38	-9.12	20.72×10^{4}
FO7	-83.06	-8.40	69.50×10^{4}
FO8	-79.73	-7.98	15.50×10^{5}
FO13	-80.71	-7.46	33.73×10^{5}
FO14	-80.19	-7.70	22.80×10^{5}
FO17	-89.58	-8.57	30.23×10^{4}
FO18	-80.87	-8.07	12.23×10^{5}

Table 4. Comparison of Receptor-Ligand Interactions from Docking Results

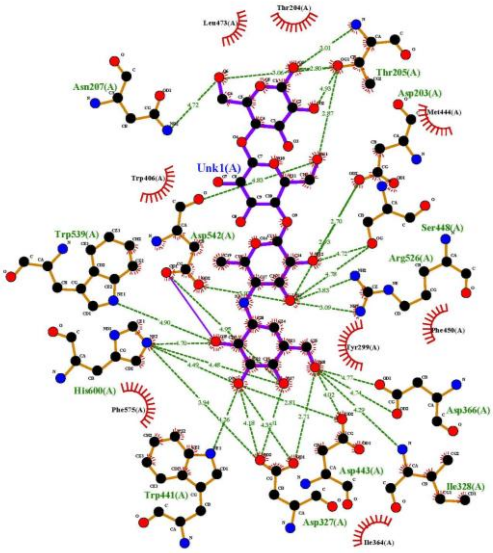
Ligands	PLANTS		YASARA STRUCTURE	
	Amino Acid Residue			
	Hydrogen Bonds	Hydrophobic Bonds	Hydrogen Bonds	Hydrophobic Bonds
Acarbose re-docked	Asp203, Thr205, Asn207, Asp327, Ile328, Asp366, Trp441, Asp443, Ser448, Arg526, Trp539, Asp542, His600	Thr204, Tyr299, Ile364, Trp406, Met444, Phe450, Leu473, Phe575	Asp203, Thr205,Asp327, Arg526, Asp542, Thr544, His600, Tyr605	Tyr299, Ile328, Ile364, Trp406, Trp441, Asp443, Met444, Trp539, Phe575, Ala576, Leu577
FO2	Asp327, Asp443, Met444, Asp542, Arg526, Gln603	Tyr299, Ile328, Trp406, Phe450, Phe575, Gly602, Tyr605	Thr205, Asp327, Asp443, Arg526, His600	Asp203, Thr204, Tyr299, Ile364, Trp406, Trp441, Met444, Trp539, Asp542, Phe575, Gln603
FO3	Asp203, Tyr299, Phe450, Arg526, Asp542, Gln603	Trp406, Met444, Ly480, Phe575	Asp443, Arg526, His600, Tyr605	Asp203, Tyr299, Asp327, Ile328, Ile364, Trp406, Trp441, Met444, Trp539, Asp542, Phe575, Gln603
FO7	Asp327, Asp443, Met444, Arg562, Asp542, Gln603	Tyr299, Ile328, Trp406, Phe450, Phe575, Gly602, Tyr605	Thr205, Asp327, Asp443, Arg526, His600	Asp203, Thr204, Tyr299, Ile364, Trp406, Trp441, Met444, Trp539, Asp542, Phe575, Gln603
FO17	Asp203, Tyr214, Asp443, Arg526, Asp542, Gln603, Tyr605	Thr204, Thr205, Pro206, Tyr299, Trp406, Met444, Phe575, Gly602	Tyr299, Asp327, Trp406, Asp443, Met444, Phe450, Asp542, Phe575, Gly602	Asp203, Arg526, His600, Gln603, Tyr605

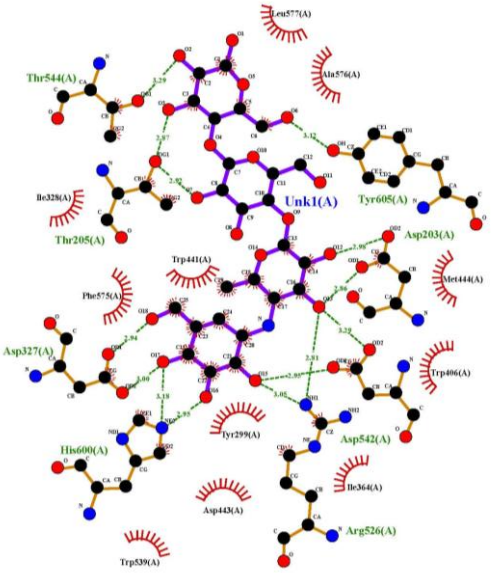
Description: Yellow residues indicate the active site of the protein, while turquoise residues indicate the catalytic site of the protein.

The interaction analysis showed that although ligands exhibited distinct interaction patterns, most compounds bound to common residues, implying a shared binding site. Both docking programs consistently identified Tyr299 and Asp542 as key anchoring residues. Among all test ligands, only FO3 in the PLANTS docking did not interact with the catalytic residue Asp443; all other ligands interacted with at least one catalytic residue via hydrogen bonding or hydrophobic interactions.

Additionally, PLANTS predicted interactions with Phe450 for all ligands except FO17, while YASARA predicted Phe450 involvement only in FO17.

a





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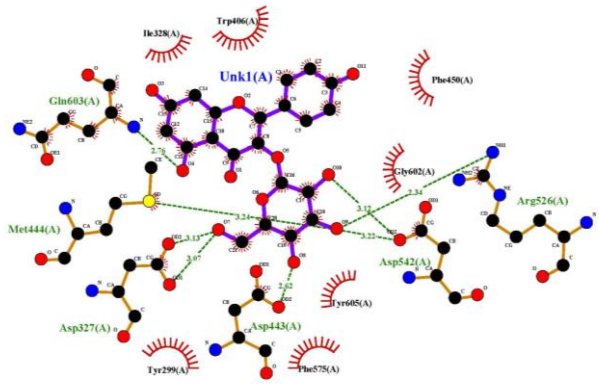

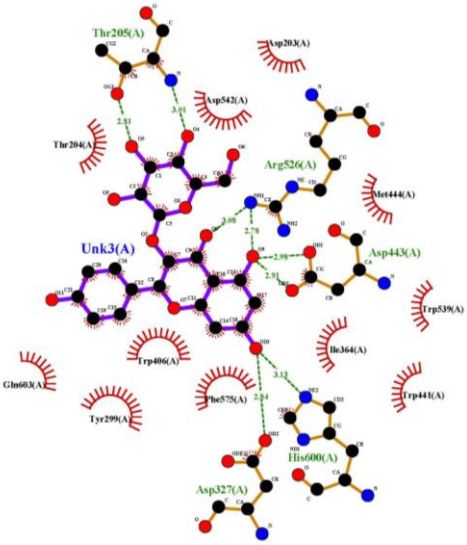

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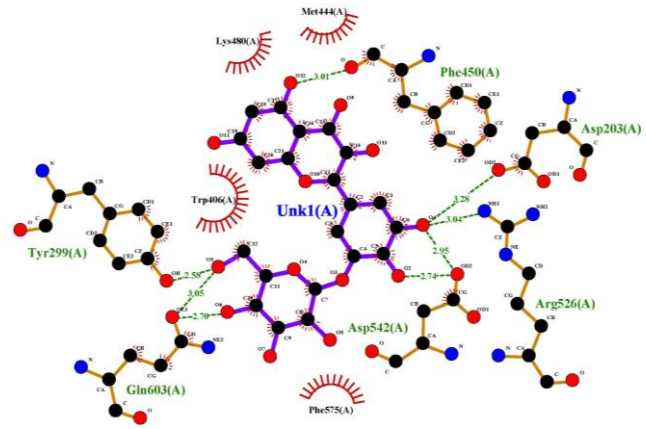

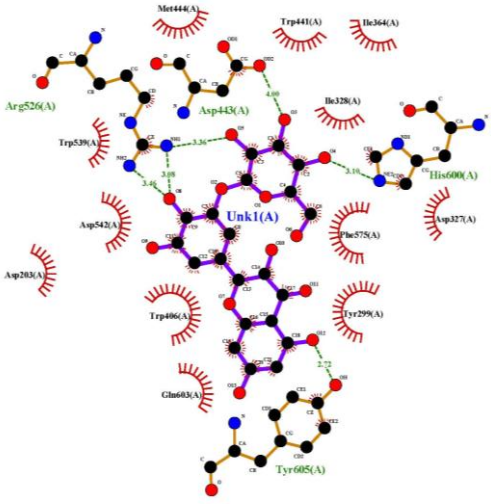

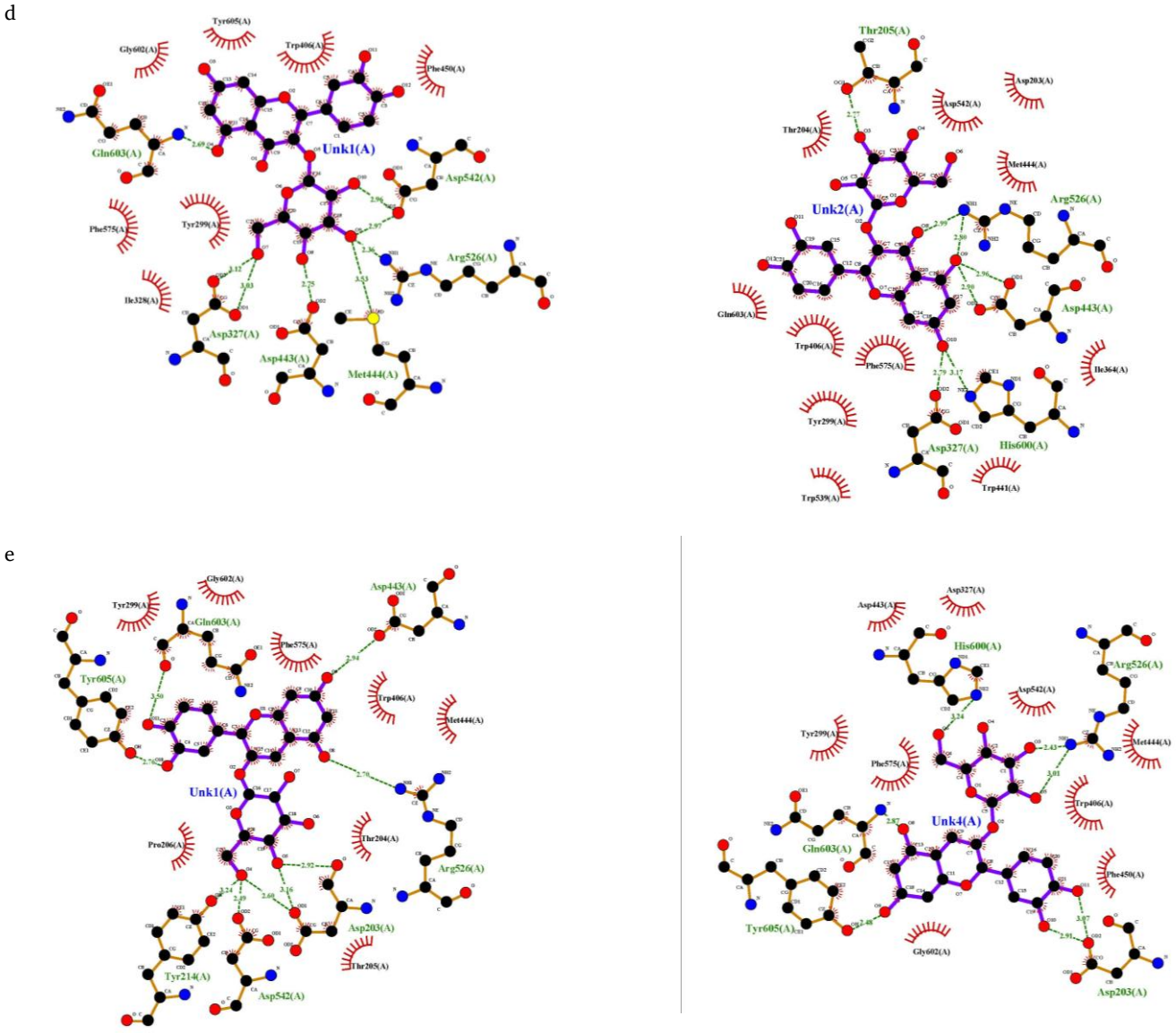

Figure 3. 2D Visualization of Molecular Docking Results using PLANTS (left) and YASARA Structure (right) (a) Acarbose, (b) Kaempferol-3-O-glucoside (FO2), (c) Cannabiscitrin (FO3), (d) Isoquercetin (FO7), (e) Cyanidin 3-glucoside (FO17).

4. CONCLUSION

Molecular docking of seven phenolic acids and twenty flavonoid compounds identified in okra (*Abelmoschus esculentus*L.) using the PLANTS and YASARA Structure platforms identified four top-performing ligands: kaempferol-3-O-glucoside, cannabiscitrin, isoquercetin, and cyanidin-3-glucoside. Among these, cannabiscitrin showed lower ΔG, Kd, and docking scores compared with the reference compound, acarbose, and demonstrated a superior physicochemical profile. These findings indicate that cannabiscitrin possesses the most promising drug-like properties and may serve as a potential alternative antidiabetic agent.

AUTHOR CONTRIBUTIONS

L.A. contributed to the conceptualization, supervision, and review the manuscript. S.N.A. was responsible for methodology, software development, validation and visualization, investigation, review and editing of the manuscript. F.A. carried out the formal analysis, data curation, and write the original draft. All authors have read and agreed to the published version of the manuscript.

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Not applicable.

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

No new data were created or analyzed in this study. Data sharing is not applicable.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) USE

The authors declare that no generative AI or AI-assisted technologies were used in the preparation or writing of this manuscript. All contents were produced entirely by the authors without any automated assistance.

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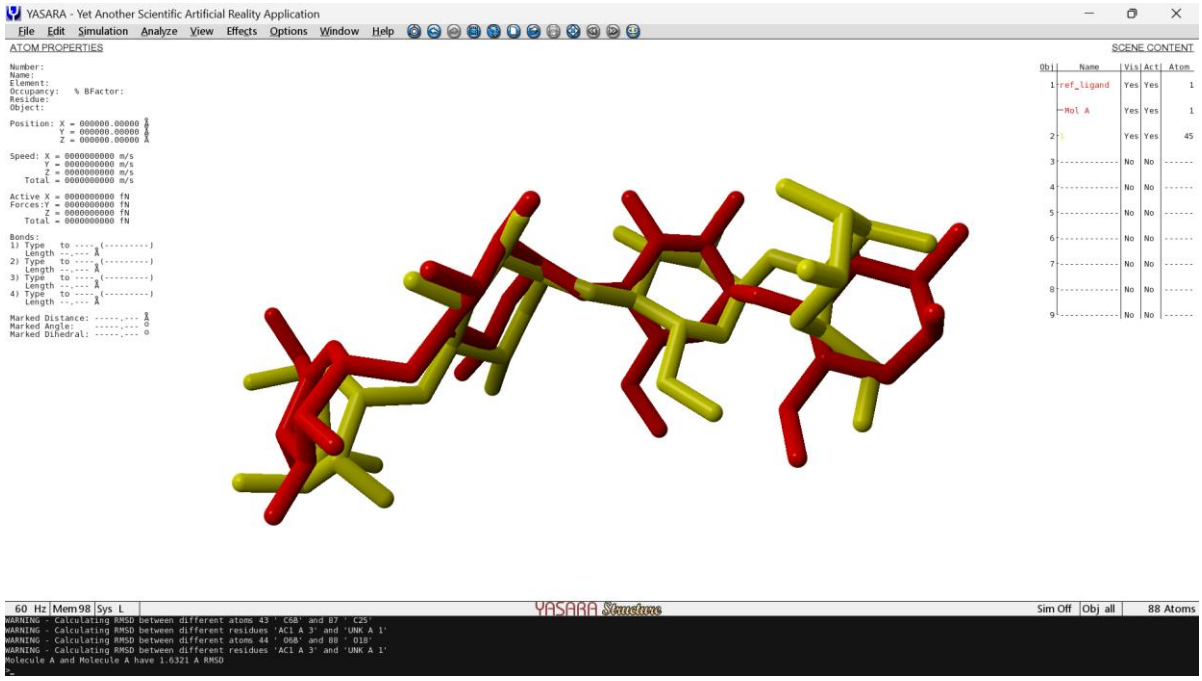
Appendix 1. RMSD Result

a



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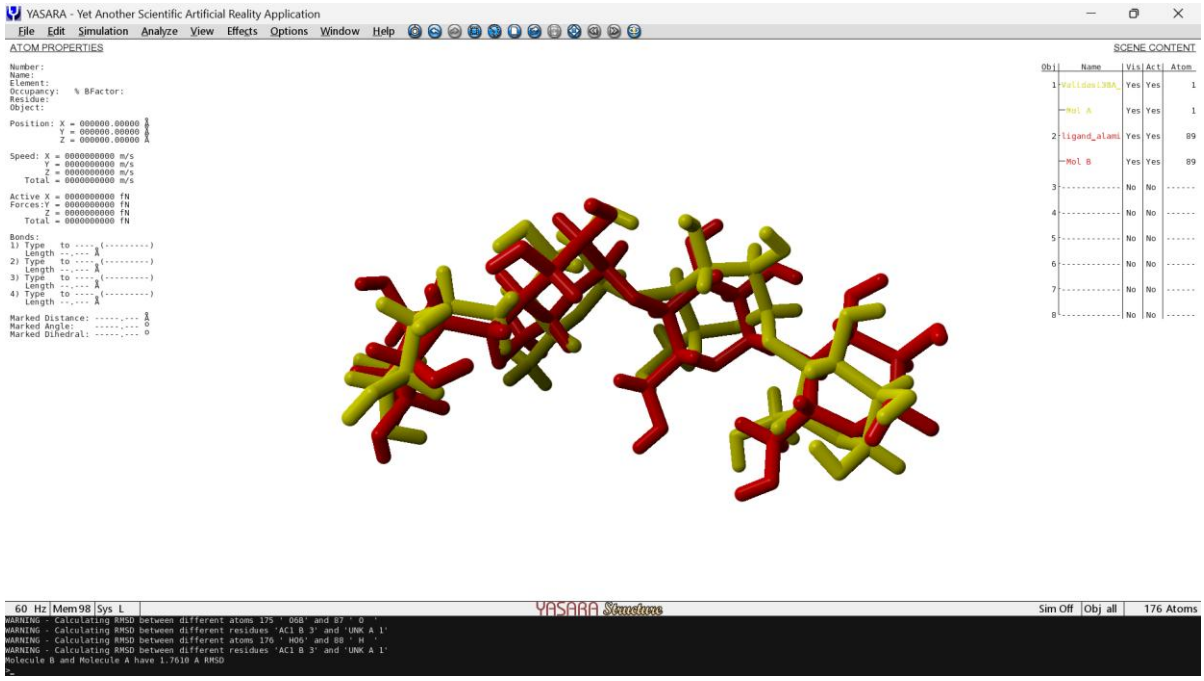

Figure 4. RMSD result a) PLANTS b) YASARA Structure