

Molecular Docking Analysis Of Phenolic and Flavonoid Compounds from *Eichhornia Crassipes* for Antidiabetic Activity Through Interaction with PPAR- γ (5Y2O) and α -Glucosidase (3TOP)

Khoirunnisa Muslimawati^{1*}, Taufik Muhammad Fakhri², Nabila Hadiah Akbar¹, Aditya Maulana Perdana Putra³, Nazhipah Isnani³

¹Pharmacist Professional Education Study Program, Faculty of Mathematics and Natural Sciences, Universitas Lambung Mangkurat, South Kalimantan, Indonesia

²Pharmacist Professional Education Study Program, Faculty of Mathematics and Natural Sciences, Universitas Islam Bandung, West Java, Indonesia

³Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Lambung Mangkurat, South Kalimantan, Indonesia

Email: khoirunnisamuslimawati@ulm.ac.id

ABSTRAK

*Diabetes Mellitus Tipe 2 (DMT2), ditandai dengan resistensi insulin dan hiperglikemia. Penelitian ini mengevaluasi potensi 30 senyawa golongan fenolik dan flavonoid dari *Eichhornia crassipes* sebagai agen antidiabetes melalui studi in silico, meliputi uji toksisitas (ToxTree 3.1.0, ProTox 3), analisis ADME (SwissADME), dan molecular docking (AutoDock 4.2.6). Struktur ligan uji diperoleh dari PubChem, sedangkan reseptor PPAR- γ (PDB ID: 5Y2O) dan α -Glukosidase (PDB ID: 3TOP) diunduh dari RCSB Protein Data Bank. Sebelum docking, analisis toksisitas dan ADME dilakukan. Hasil docking menunjukkan Tricin (flavonoid) berinteraksi baik dengan kedua reseptor dan memiliki nilai energi Gibbs -7.53 kcal/mol untuk PPAR- γ dan -5.19 kcal/mol untuk α -Glukosidase, mendekati ligan asli Pioglitazone (-10.03 kcal/mol) dan Acarbose (-6.86 kcal/mol). Interaksi ligan-reseptor Tricin melibatkan ikatan hidrogen dan kontak hidrofobik dengan residu kunci (misalnya, ARG288 dan TYR pada PPAR- γ , residu GLN1561 dan GLN1372 pada α -Glukosidase), mencerminkan interaksi ligan asli. Prediksi toksisitas mengklasifikasikan Tricin sebagai senyawa dengan risiko toksisitas rendah (Cramer Rules Kelas I, Kroes TTC). Selanjutnya, evaluasi ADME menunjukkan bahwa Tricin memenuhi Lipinski's Rule of Five, yang mengindikasikan penyerapan dan bioavailabilitas oral yang baik. Secara keseluruhan, senyawa Tricin dari *E. crassipes* menunjukkan potensi signifikan sebagai kandidat agen antidiabetes melalui penghambatan PPAR- γ dan α -Glukosidase yang selanjutnya memerlukan validasi dengan pengujian in vitro dan in vivo.*

Kata Kunci: *Eichhornia crassipes*, Molecular Docking, Antidiabetic, PPAR- γ , α -Glucosidase

ABSTRACT

Type 2 Diabetes Mellitus (T2DM), is characterized by insulin resistance and persistent hyperglycemia. This study investigated the antidiabetic potential of 30 phenolic and flavonoid compounds derived from *Eichhornia crassipes* using in silico approaches, including toxicity assessments (ToxTree 3.1.0, ProTox 3), ADME analysis (SwissADME), and molecular docking (AutoDock 4.2.6). Ligand structures were retrieved from PubChem, while PPAR- γ (5Y2O) and α -Glucosidase (3TOP) receptors were obtained from the RCSB Protein Data Bank. Toxicity and ADME analyses were conducted prior to molecular docking, which employed the Genetic Algorithm with 50 conformations. Docking results revealed that Tricin (a flavonoid) exhibited strong interactions with both receptors, with Gibbs free energy values of -7.53 kcal/mol for PPAR- γ and -5.19 kcal/mol for α -Glucosidase. These values are comparable to those of the native ligands Pioglitazone (-10.03 kcal/mol) and Acarbose (-6.86 kcal/mol). Tricin formed hydrogen bonds and hydrophobic contacts with key active site residues including, ARG288 and TYR327 in PPAR- γ , GLN1561 and GLN1372 in α -Glucosidase), mirroring the interactions of the native ligands. Toxicity predictions classified Tricin as low risk (Class I Cramer Rules, Kroes TTC). Furthermore, ADME evaluation showed that Tricin (aglycone) is fully compliant with Lipinski's Rule of Five, suggesting favorable properties for oral absorption and bioavailability. In conclusion, Tricin from *E. crassipes* demonstrates significant potential as an antidiabetic candidate and warrants further in vitro and in vivo validation.

Keywords: *Eichhornia crassipes*, Molecular docking, Antidiabetic, PPAR- γ , α -Glucosidase

I. INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by elevated blood glucose levels (hyperglycemia) due to insulin deficiency, insulin resistance, or a combination of both, leading to various health complications (Ganugapati et al., 2012; Rao & Hariprasad, 2021). With a continuously rising global prevalence, DM particularly Type 2 Diabetes Mellitus (T2DM), has become a critical public health concern, primarily marked by insulin resistance and pancreatic beta-cell dysfunction (Kumar et al., 2007). Current DM therapies involve multiple approaches, including

pharmacotherapeutic agents that target specific metabolic pathways (American Diabetes Association, 2024). Two important therapeutic targets in T2DM management are Peroxisome Proliferator-Activated Receptor gamma (PPAR- γ) and α -Glucosidase.

PPAR- γ , a nuclear hormone receptor, plays a key role in regulating glucose homeostasis, lipid metabolism, and adipocyte function (Lee et al., 2017). Activation of PPAR- γ by its agonists, such as thiazolidinedione (TZD) class of drugs (e.g., lobeglitazone and pioglitazone), improves glucose uptake, enhances insulin signaling, and increases insulin sensitivity,

making it an attractive target for T2DM (Kumar et al., 2007; Lee et al., 2017). Conversely, α -Glucosidase, an enzyme located at the brush border of the small intestine is responsible for hydrolyzing oligosaccharides and disaccharides into absorbable monosaccharides (e.g., glucose). Inhibition of α -Glucosidase slows glucose absorption from dietary carbohydrates, thereby reducing post-prandial blood glucose spikes (Ren et al., 2011).

The aquatic plant *Eichhornia crassipes* (water hyacinth), despite being recognized as an invasive weed, exhibits various pharmacological activities, including antidiabetic, antioxidant, and antimicrobial effects (Sanmuga Priya & Senthamil Selvan, 2017; Soliman et al., 2023). Previous studies have shown its antidiabetic potential; for instance, the methanolic extract of the *E. crassipes* demonstrated significant blood glucose reduction and antioxidant activity in streptozotocin-induced rats at doses of 200 and 400 mg/kg body weight (Raju et al., 2021). Additionally, methanol extract of water hyacinth have shown *in vitro* α -amylase inhibitory activity, suggesting its role in controlling post-prandial glucose levels (Awote et al., 2021). Ethanol extract of water hyacinth leaves, both individually and combined with *Sintrong* leaves, also exhibited notable hypoglycemic effects in

alloxan-induced mice, with the presence of flavonoids, saponins, polyphenols, and tannins believed to contribute to its activity (Priyoherianto et al., 2020). Earlier preliminary studies have further attributed the hypoglycemic properties of *E. crassipes* to its rich content of flavonoid and phenolic compounds. Therefore, the scope of this *in silico* study was specifically focused on 30 compounds from the flavonoid and phenolic classes, as these groups are considered the primary active constituents responsible for the plant's documented antidiabetic activity (Raju et al., 2021). To structurally validate this observed antidiabetic potential and predict the compounds' mechanism of action, a computational approach is necessary.

The utilization of Computer-Aided Drug Design (CADD), specifically the *in silico* approach, has become an indispensable method for accelerating the drug discovery pipeline by dramatically reducing associated time and costs (Chang et al., 2023; Leelananda & Lindert, 2016). Molecular docking serves as the primary computational strategy, predicting the optimal conformation and binding energy of a small-molecule ligand within a receptor's active site to assess its potential efficacy (Naglah et al., 2020). A foundational requirement for this method is protocol validation, often achieved by re-

docking the native ligand and confirming that the calculated pose results in a RMSD of less than 2 against the crystallographic structure (Shamsian et al., 2024).. Furthermore, the initial virtual screening process is now routinely integrated with robust *in silico* ADME and Toxicity (Tox) profiling. These predictions allow for the early evaluation of pharmacokinetic suitability and safety hazards, effectively filtering out compounds likely to fail due to poor bioavailability or adverse effects (Ancuceanu et al., 2025; Durán-Iturbide et al., 2020; Listyani et al., 2022). This comprehensive, multi-step computational strategy ensures a high-quality selection of drug candidates for subsequent *in vitro* testing.

Molecular docking, as employed in this *in silico* study, is a computational approach that predicts binding affinities and ligand-receptor interaction modes, facilitating the identification of compounds with therapeutic potential (Kumar et al., 2007; Rao & Hariprasad, 2021; Zetta et al., 2025). Besides efficacy, ADME (Absorption, Distribution, Metabolism, Excretion) profiles and toxicity are essential factors in drug development, with Lipinski's Rule of Five commonly used to assess drug-likeness (Ganugapati et al., 2012). In this research, molecular docking analysis was performed on 30 phytochemical compounds from the

flavonoid and phenolic classes identified in *Eichhornia crassipes* to evaluate their potential as antidiabetic agents through the inhibition of the PPAR- γ receptor (PDB ID: 5Y2O) and α -Glucosidase (PDB ID: 3TOP). This approach aims to provide structural insights into ligand-protein interactions and identify promising antidiabetic candidates from water hyacinth with favorable efficacy and safety profiles. Ultimately, this study aims to identify the most potent antidiabetic candidate from *Eichhornia crassipes* for further *in vitro* and *in vivo* validation as a dual inhibitor of PPAR- γ and α -Glucosidase.

II. METHOD

A. Material

The three-dimensional structures of the PPAR- γ receptor (PDB ID: 5Y2O) and α -Glucosidase (PDB ID: 3TOP) were retrieved from the Protein Data Bank (PDB) database (www.rcsb.org), as detailed in Table I. Thirty phytochemical compounds belonging to the Phenolic and Flavonoid classes, previously identified from *Eichhornia crassipes*, were selected as test ligands for this study. The three-dimensional structures of these compounds were obtained from the PubChem.

The computational analyses were performed on an ASUS laptop equipped with an AMD Ryzen 5 5600H Processor with Radeon Graphics, 16GB RAM, and a

64-bit operating system. The software utilized for this research included Autodock 1.5.7 (Morris et al., 2009), PyMOL 3.1.6.1 (Schrödinger, 2025), BIOVIA Discovery Studio Visualizer 25.1.0 (BIOVIA Dassault Systèmes., 2025), Avogadro 1.2.0 (Hanwell et al., 2012), ToxTree 3.1.0 (Patlewicz et al., 2008), SwissADME (Daina et al., 2017), and Protox 3.0 (Banerjee et al., 2018).

Table I. Antidiabetic Receptors and Their Native Ligands

Receptor	Native Ligand	Referensi
PPAR- γ (5Y2O)	Pioglitazone	(Lee et al., 2017)
α -Glukosidase (3TOP)	Acarbose	(Ren et al., 2011)

B. Receptor and Ligand Preparation

Prior to the docking simulations, the protein structures were prepared by removing water molecules, native ligands, and non-protein cofactors. The three-dimensional (3D) structures and SMILES strings of the thirty phenolic and flavonoid compounds identified from *Eichhornia crassipes* were retrieved from the PubChem (available online at: <https://pubchem.ncbi.nlm.nih.gov/>).

C. Analysis in Silico Toxicity & ADME

In silico toxicity analysis was conducted using the Toxtree 3.1.0 software (based on Cramer rules and Kroes TTC) and the ProTox 3.0 website to assess the

potential toxicity of the test compounds. Subsequently, pharmacokinetic analysis was performed using Lipinski's Rule of Five criteria via the SwissADME website. All analyses were conducted by inputting the test ligand structures in SMILES format.

D. Molecular Docking

Molecular docking simulations were performed using AutoDock 4.2.6 software. The docking parameters are presented in Table II. The docking protocol was validated by re-docking the native ligands: Pioglitazone (PDB ID: 8N6) for 5Y2O and Alpha-Acarbose (PDB ID: PRD) for 3TOP. The Root Mean Square Deviation (RMSD) between the re-docked and co-crystallized conformations was calculated to ensure the accuracy of the docking method. Following validation, the 30 selected phytochemical compounds were docked into the active sites of PPAR- γ (PDB ID: 5Y2O) and α -Glucosidase (PDB ID: 3TOP). The resulting binding affinities (binding energy) were recorded and utilized as the primary criterion for evaluating their potential inhibitory activity.

III. RESULTS AND DISCUSSION

The preliminary safety profile phenolic and flavonoid compounds was investigated through in silico toxicity

prediction using the ToxTree and ProTox-II platforms. These assessments are critical for validating the potential clinical development of any natural product-derived compound.

The ToxTree analysis, which applies the Cramer and Verhaar schemes, classified the majority of the compounds, including Tricin, as belonging to Toxicity Class III (Low) (Cramer rules) and Class A (Negligible risk) (Kroes TTC*). This classification suggests that Tricin is predicted to have a low acute toxicity risk, indicating a relatively favorable safety margin.

Furthermore, the ProTox-II analysis provided a comprehensive evaluation of various toxicological endpoints, which is summarized in Table V. Specifically, Tricin was predicted to be non-toxic in key endpoints, including Hepatotoxicity and Carcinogenicity, and was assigned an Oral Toxicity Class of 5 (LD₅₀ 2000 - 5000 mg/kg). This classification indicates a low level of acute oral toxicity and is consistent with the generally safe nature of natural flavonoid compounds.

These robust *in silico* findings strongly suggest that the antidiabetic potential of Tricin is not counteracted by severe safety concerns. The predicted low acute toxicity and favorable profiles across critical toxicological parameters support the advancement of Tricin into subsequent

in vitro and *in vivo* efficacy and safety studies. The RMSD for the overlay of the native ligand and re-docked conformation was 0.500 Å for the PPAR- γ receptor and 0.414 Å for the α -Glucosidase receptor. These values, being below 2 Å, indicate that the established docking parameters are valid for screening test ligands. The RMSD values, docking parameters, and visualization details can all be found in Table II.

In structure-based molecular docking, the ligand is positioned within the binding pocket of the target protein, and the resulting docking poses are evaluated using a scoring function, which assigns a score to each pose and ranks them accordingly (Pantsar & Poso, 2018). Based on the docking data (Table V), the native ligand receptor PPAR- γ (5Y2O), Pioglitazone exhibited a Gibbs free energy of -10.03 kcal/mol, while receptor α -Glucosidase (3TOP) with Alpha-Acarbose showed a value of -6.86 kcal/mol. A more negative Gibbs free energy indicates a stronger binding affinity between the ligand and the receptor, suggesting a higher inhibitory potential. Among the tested compounds, Tricin demonstrated the high binding affinity for both receptors, suggesting a higher inhibitory potential, with values of -7.53 kcal/mol for PPAR- γ (5Y2O) and -5.19 kcal/mol for α -

glucosidase (3TOP). While the Gibbs free energy values of Tricin were still less negative compared to those of the native ligands, Pioglitazone and Alpha-Acarbose, it was the best-performing compound in the library. Other flavonoid compounds, such as Azaleatin, Chrysoeriol, and Luteolin, also exhibited promising binding affinities. Overall, flavonoid compounds showed better binding affinities compared to phenolic compounds.

The superior results for Tricin across both the Gibbs free energy for the two key antidiabetic targets (5Y2O and 3TOP) and its highly favorable in silico toxicity (Class 5/Low) and druglikeness profile (0 violations in SwissADME) strongly position it as the most promising candidate for further development as an antidiabetic agent from this compound library.

A. Ligand-Receptor Interaction Analysis

1. PPAR- γ (5Y2O)

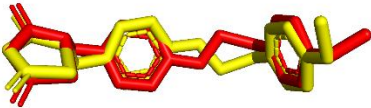
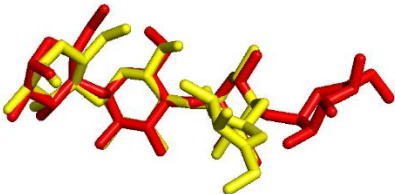
Pioglitazone, the native ligand for PPAR- γ , exhibits a strong binding affinity with a Gibbs free energy of -10.03 kcal/mol, forms multiple hydrophobic interactions

2. Alpha-Glucosidase (3TOP)

Alpha-Acarbose, a well-known competitive α -Glucosidase inhibitor, exhibited a Gibbs free energy of -6.86 kcal/mol. This inhibitor functions by preventing the breakdown of

complex carbohydrates in the intestine. Crystallographic studies of human intestinal maltase-glucoamylase (MGAM) reveal that 21 amino acids within the active site of MGAM-C create additional sugar-binding subsites, designated as +2 and +3. Furthermore, the substitution of Trp1251 to tyrosine in MGAM-C confers the enzyme with the ability to hydrolyze α -1,6-linked branched oligosaccharides, emphasizing the critical role of Trp1251 in enzymatic activity (Ren et al., 2011). Tricin demonstrated a Gibbs free energy of -5.19 kcal/mol against α -Glucosidase (3TOP). Its interaction pattern closely resembles Acarbose (PRD), particularly through several types of bonding: Conventional Hydrogen Bonds (with GLN1561 and GLN1372), Pi-Donor Hydrogen Bonds (with GLC1 and GLC2), Pi-Sigma (with ILE1587), and Pi-Pi T-shaped (with TRP1369 and PHE1560). These interactions, which involve key π -stacking residues like TRP1369 and PHE1560, suggest that Tricin can bind to the active site of α -Glucosidase at a position identical or overlapping with Acarbose, thereby potentially inhibiting enzyme activity. The planar structure of the flavonoid, coupled with its hydroxyl and methoxy groups, facilitates the formation of multiple hydrogen bonds and strong π -stacking interactions, a key factor contributing to its binding affinity (Figure 2).

Table II. Docking Parameters and Re-Docking Results

Receptor	Visualisasi Overlay	Parameter	RMSD
5Y2O (Native ligand: Pioglitazone)		Grid box: -48.382; -1.335; 77.313 Spacing: 0,375 Genetic Algorithm Population size 300 Num of evals 2500000 Num of generations 27000 Konformasi 50	0,500
3TOP (Native ligand: Acarbose)		Grid box: -52.362; 9.162; -64.514 Spacing 0,375 Genetic Algorithm Population size 300 Num of evals 2500000 Num of generations 27000 Konformasi 50	0,414

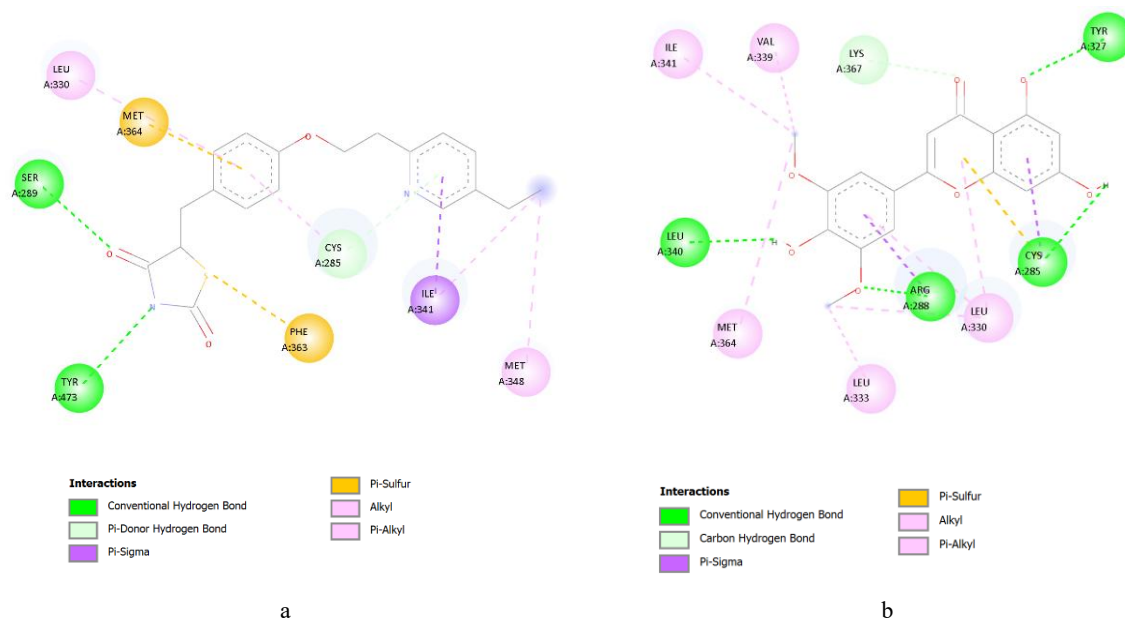
Notes: Red: Native ligand; Yellow: Re-docked conformation

Table III. PPAR- γ (5Y2O) interaction with Pioglitazone (8N6) and Tricin

Ligand	Name	Category
Pioglitazone (8N6)	SER289 - 8N6501:O4	Conventional Hydrogen Bond
	8N6501:N3 - TYR473:OH	Conventional Hydrogen Bond
	CYS285 - 8N6501	Pi-Donor Hydrogen Bond;Pi-Sulfur
	ILE341 - 8N6501	Pi-Sigma
	MET364 - 8N6501	Pi-Sulfur
	8N6501:S1 - PHE363	Pi-Sulfur
	8N6501:C24 - ILE341	Alkyl
	8N6501:C24 - MET348	Alkyl
	8N6501 - CYS285	Pi-Alkyl
	8N6501 - LEU330	Pi-Alkyl
Tricin	ARG288:HH11 - UNL1	Conventional Hydrogen Bond
	TYR327:HH - UNL1	Conventional Hydrogen Bond
	UNL1 - LEU340:O	Conventional Hydrogen Bond
	UNL1 - CYS285:O	Conventional Hydrogen Bond
	ARG288:HD2 - UNL1	Carbon Hydrogen Bond
	LYS367:HE1 - UNL1	Carbon Hydrogen Bond
	CYS285:HB2 - UNL1	Pi-Sigma
	ARG288:HG1 - UNL1	Pi-Sigma
	CYS285:SG - UNL1	Pi-Sulfur
	UNL1 - VAL339	Alkyl
	UNL1 - ILE341	Alkyl
	UNL1 - MET364	Alkyl
	UNL1 - LEU330	Alkyl
	UNL1 - LEU333	Alkyl
	UNL1 - LEU330	Pi-Alkyl

Table IV. Alpha-Glucosidase (3TOP) interaction with Acarbose (PRD) and Tricin

Ligand	Name	Category
Acarbose (PRD)	LYS1164 - GLC1:O2	Conventional Hydrogen Bond
	LYS1460 - GLC2:O2	Conventional Hydrogen Bond
	ARG1510 - AC13:O3	Conventional Hydrogen Bond
	ARG1510 - AC13:O2B	Conventional Hydrogen Bond
	GLC2:O3 - D:AC13:O2	Conventional Hydrogen Bond
	AC13:O2 - ASP1157	Conventional Hydrogen Bond
	AC13:O3 - ASP1157	Conventional Hydrogen Bond
	AC13:O3 - MET1421	Conventional Hydrogen Bond
	AC13:N4A - ASP1526	Conventional Hydrogen Bond
	AC13:O2B - ASP1526	Conventional Hydrogen Bond
	AC13:O4 - ASP1279	Conventional Hydrogen Bond
	AC13:O4 - HIS1584	Conventional Hydrogen Bond
	AC13:C2B - ASP1420	Carbon Hydrogen Bond
	AC13:C6B - ASP1279	Carbon Hydrogen Bond
	GLC1:O6 - PHE1560	Pi-Donor Hydrogen Bond
	PHE1559 - AC13:C	Pi-Alkyl
	PHE1560 - AC13:C	Pi-Alkyl
Tricin	GLN1561:N - UNL1	Conventional Hydrogen Bond
	UNL1:H - GLN1372:OE1	Conventional Hydrogen Bond
	GLC1:O6 - UNL1	Pi-Donor Hydrogen Bond
	GLC2:O6 - UNL1	Pi-Donor Hydrogen Bond
	ILE1587:CG2 - UNL1	Pi-Sigma
	TRP1369 - UNL1	Pi-Pi T-shaped
	PHE1560 - UNL1	Pi-Pi T-shaped
	UNL1 - AC13:C6	Pi-Alkyl

**Figure 1.** Visualization of PPAR- γ (5Y2O) interaction with (a) Pioglitazone (8N6) and (b) Tricin

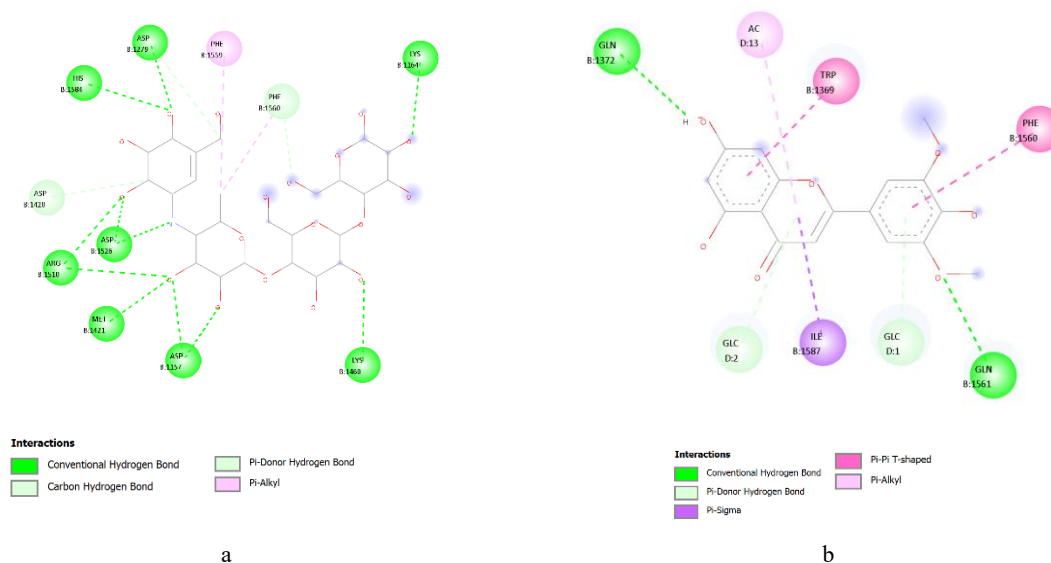


Figure 2. Visualization of Alpha-Glucosidase (3TOP) interaction with (a) Acarbose (PRD) and (b) Tricin

Table V. Gibbs Energy Values and in silico Toxicity and ADME Analysis

Namw	Group	Protox	Toxicity Toxtree		Res ult	SwissADME	Gibbs Energy	
			Crame r rules*	Kroe s TTC **			5Y2O	3TOP
Pioglitazone (8N6)	Native Ligand 5Y2O						-10.03	
Alpha-Acarbose (PRD)	Native Ligand 3TOP							-6.86
2-Methylresorcinol	Fenol	Class 3	Low	A	safe	Yes; 0 violation	-5.27	-3.81
4-Methylresorcinol	Fenol	Class 3	Low	A	safe	Yes; 0 violation	-5.35	-4.25
Catechol	Fenol	Class 3	Low	A	safe	Yes; 0 violation	-5.26	-3.45
Resorcinol	Fenol	Class 3	Low	A	safe	Yes; 0 violation	-4.99	-4.13
p-Hydroxybenzoic acid	Fenol	Class 5	Low	A	safe	Yes; 0 violation	-4.75	-4.20
Gentisic acid	Fenol	Class 5	Low	A	safe	Yes; 0 violation	-5.40	-3.88
Chlorogenic acid	Fenol	Class 5	Interme diate	A	safe	Yes; 1 violation: NHorOH>5	-7.00	-4.10
Caffeic acid	Fenol	Class 5	Low	A	safe	Yes; 0 violation	-5.71	-3.55
p-Coumaric acid	Fenol	Class 5	Low	A	safe	Yes; 0 violation	-5.52	-3.70
Ferulic acid	Fenol	Class 4	Low	A	safe	Yes; 0 violation	-5.47	-3.78
Vanillic acid	Fenol	Class 4	Low	A	safe	Yes; 0 violation	-4.73	-3.52
Gallic acid	Fenol	Class 4	Low	A	safe	Yes; 0 violation	-4.57	-3.44
Syringic acid	Fenol	Class 4	Low	A	safe	Yes; 0 violation	-4.16	-3.02
Salicylic acid	Fenol	Class 4	Low	A	safe	Yes; 0 violation	-5.20	-4.27
Protocatechuic acid	Fenol	Class 4	High	A	safe	Yes; 1 violation: MLOGP>4.15	-6.23	-4.27
Pyrogallol	Fenol	Class 3	Low	A	safe	Yes; 0 violation	-4.82	-3.53

Namw	Group	Protox	Toxicity Toxtree		Res ult	SwissADME	Gibbs Energy	
			Cramer rules*	Kroes TTC **			5Y2O	3TOP
Gossypetin	Flavonoid	Class 3	High	A	safe	Yes; 1 violation: NHorOH>5	-6.47	-4.55
Tricin	Flavonoid	Class 5	High	A	safe	Yes; 0 violation	-7.53	-5.19
Azaleatin	Flavonoid	Class 5	High	A	safe	Yes; 0 violation	-6.92	-5.53
Chrysoeriol	Flavonoid	Class 5	High	A	safe	Yes; 0 violation	-7.49	-5.35
Luteolin	Flavonoid	Class 5	High	A	safe	Yes; 0 violation	-7.14	-5.90
Apigenin	Flavonoid	Class 5	High	A	safe	Yes; 0 violation	-7.09	-5.79
Orientin	Flavonoid	Class 4	High	A	safe	No; 2 violations: NorO>10, NHorOH>5	-8.12	-4.37
Kaempferol	Flavonoid	Class 5	High	A	safe	Yes; 0 violation	-6.33	-5.53
Quercetin	Flavonoid	Class 3	High	A	safe	Yes; 0 violation	-6.27	-5.10
Isovitexin	Flavonoid	Class 3	High	A	safe	Yes; 1 violation: NHorOH>5	-5.61	-3.95
Naringenin	Flavonoid	Class 4	High	A	safe	Yes; 0 violation	-7.25	-5.78
Myricetin	Flavonoid	Class 3	High	A	safe	Yes; 1 violation: NHorOH>5	-6.00	-4.58
Rutin	Flavonoid	Class 5	High	A	safe	No; 3 violations: MW>500, NorO>10, NHorOH>5	-6.02	-3.80
Rhamnetin	Flavonoid	Class 5	High	A	safe	Yes; 0 violation	-6.68	-5.33

Notes:

*Cramer rules (Class I: Low; Class II: Intermediate; Class III: High)

**Kroes TTC (A: Substance would not be expected to be a safety concern; B: Negligible risk; C: Risk assessment requires compound-specific toxicity data)

IV.CONCLUSION

This study demonstrates that phenolic and flavonoid compounds derived from *Eichhornia crassipes*, particularly Tricin, exhibit promising antidiabetic potential through the inhibition of PPAR- γ (5Y2O) and α -glucosidase (3TOP) receptors. Molecular docking results

revealed that Tricin exhibited Gibbs free energy of -7.53 kcal/mol for PPAR- γ (5Y2O) and -5.19 kcal/mol for α -glucosidase (3TOP), indicating a relatively strong binding affinity, although slightly lower than the native ligands Pioglitazone and Acarbose. Tricin's interaction involved hydrogen bonding and hydrophobic

contacts with key active site residues, displaying interaction patterns similar to those of the native ligands. Furthermore, in silico toxicity analysis classified Tricin as a low-risk compound. Importantly, Tricin (aglycone) is fully compliant with Lipinski's Rule of Five, possessing favorable molecular weight (330.3 g/mol), 3 H-bond donors, and 7 H-bond acceptors, which suggests good potential for oral bioavailability. Overall, Tricin demonstrates strong potential as a natural antidiabetic candidate. However, further validation through in vitro and in vivo studies is essential to confirm its efficacy and safety.

CONFLICT OF INTEREST

All authors declare that there is no conflict of interest in this research.

ACKNOWLEDGEMENT

The authors would like to express their sincere gratitude to all parties who contributed to this research. Special thanks are extended to the co-authors and research collaborators for their invaluable scientific input and teamwork throughout the study.

REFERENCES

- American Diabetes Association. (2024). Improving Care and Promoting Health in Populations: Standards of Care in Diabetes—2024. *Diabetes Care*, 47, S11–S19. <https://doi.org/10.2337/dc24-S001>
- Ancuceanu, R., Lascu, B. E., Drăgănescu, D., & Dinu, M. (2025). In Silico ADME Methods Used in the Evaluation of Natural Products. *Pharmaceutics*, 17(8), 1002. <https://doi.org/10.3390/pharmaceutics17081002>
- Awote, O. K., Adeyemo, A. G., Igbalaye, J. O., Awosemo, R. B., Ibrahim, A. B., Omolaja, B. E., Abdulrafiu, F., & Fajobi, T. (2021). In Vitro Alpha-Amylase Inhibitory Activity, Antioxidant Activity and HPLC Analysis of Eichhornia crassipes (water hyacinth) Methanol Extracts. *Tropical Journal of Natural Product Research*, 5(12), 2174–2181. <https://doi.org/10.26538/tjnpr/v5i12.23>
- Banerjee, P., Eckert, A. O., Schrey, A. K., & Preissner, R. (2018). ProTox-II: a webserver for the prediction of toxicity of chemicals. *Nucleic acids research*, 46(W1), W257–W263. <https://doi.org/10.1093/Nar/Gky318>
- BIOVIA Dassault Systèmes. (2025). *BIOVIA Discovery Studio Visualizer, Release 25.1.0. San Diego: Dassault Systèmes*.
- Chang, Y., Hawkins, B. A., Du, J. J., Groundwater, P. W., Hibbs, D. E., & Lai, F. (2023). A guide to in silico drug design. *Pharmaceutics*, 15(1), 49. <https://doi.org/10.3390/pharmaceutics15010049>
- Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific reports*, 7(1), 42717. <https://doi.org/10.1038/Srep42717>
- Durán-Iturbide, N. A., Díaz-Eufracio, B. I., & Medina-Franco, J. L. (2020). In silico ADME/Tox profiling of natural products: A focus on BIOFACQUIM. *ACS omega*, 5(26),

- 16076-16084.
<https://doi.org/10.1021/acsomega.0c01581>
- Ganugapati, J., Baldwa, A., & Lalani, S. (2012). Molecular docking studies of banana flower flavonoids as insulin receptor tyrosine kinase activators as a cure for diabetes mellitus. *Bioinformation*, 8(5), 216. <https://doi.org/10.6026/97320630008216>
- Hanwell, M. D., Curtis, D. E., Lonie, D. C., Vandermeersch, T., Zurek, E., & Hutchison, G. R. (2012). Avogadro: An advanced semantic chemical editor, visualization, and analysis platform. *Journal of Cheminformatics*, 4(1), 17. <https://doi.org/10.1186/1758-2946-4-17>
- Kumar, R., Ramachandran, U., Khanna, S., Bharatam, P. V., Raichur, S., & Chakrabarti, R. (2007). Synthesis, in vitro and in silico evaluation of l-tyrosine containing PPAR α / γ dual agonists. *Bioorganic and Medicinal Chemistry*, 15(3), 1547–1555. <https://doi.org/10.1016/j.bmc.2006.06.063>
- Lee, M. A., Tan, L., Yang, H., Im, Y. G., & Im, Y. J. (2017). Structures of PPAR γ complexed with lobeglitazone and pioglitazone reveal key determinants for the recognition of antidiabetic drugs. *Scientific Reports*, 7(1). <https://doi.org/10.1038/s41598-017-17082-x>
- Leelananda, S. P., & Lindert, S. (2016). Computational methods in drug discovery. *Beilstein journal of organic chemistry*, 12(1), 2694–2718. <https://doi.org/10.3762/bjoc.12.267>
- Listyani, T. A., Fauzi, F., Siska Wardani, T., Selangor Malaysia, M., Ilmu, J., Alam, S., Program, S., & Tinggi Ilmu Kesehatan Kendal, S. (2022). In Silico ADME and Toxicity Studies of Devivative Phthalimide Compounds as Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitor INHIBITOR. *Global Health Science Group*, 3(1). <http://jurnal.globalhealthsciencegroup.com/index.php/PICNHS>
- Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S., & Olson, A. J. (2009). AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of computational chemistry*, 30(16), 2785–2791. <https://doi.org/10.1002/jcc.21256>
- Naglah, A. M., Askar, A. A., Hassan, A. S., Khatab, T. K., Al-Omar, M. A., & Bhat, M. A. (2020). Biological evaluation and molecular docking with in silico physicochemical, pharmacokinetic and toxicity prediction of pyrazolo[1,5-a]pyrimidines. *Molecules*, 25(6). <https://doi.org/10.3390/molecules25061431>
- Pantsar, T., & Poso, A. (2018). Binding Affinity via Docking: Fact and Fiction. *Multidisciplinary Digital Publishing Institute*, 23(8). <https://doi.org/10.3390/molecules23081899>
- Patlewicz, G., Jeliaskova, N., Safford, R. J., Worth, A. P., & Aleksiev, B. (2008). An evaluation of the implementation of the Cramer classification scheme in the Toxtree software. *SAR and QSAR in Environmental Research*, 19(5-6), 495–524. <https://doi.org/10.1080/10629360802083871>
- Priyoherianto, A., Suci, P. R., Rizki, P., Fatimah, C., Nur, A., Farmasi, W. A., Sehat, M., & Sidoarjo, M. (2020). Uji Aktivitas Antidiabetes Kombinasi Ekstrak Etanol Daun Eceng Gondok (*Eichhornia crassipes* (Mart.) Solms) dan Daun Sintrong (*Crassocephalum crepidioides* (Benth.) S. Moore) pada Mencit.

- Jurnal Insan Farmasi Indonesia*, 4(1), 44–53.
<https://doi.org/10.36387/jifi.v4i1.902>
- Raju, G., Tiwari, V. K., & Amala, C. (2021). Evaluation of antidiabetic activity using methanolic extract of *Eichhornia crassipes* against streptozotocin induced diabetes in rats. *Diabetes Manag*, 3(3), 65–72.
- Rao, M. M. V., & Hariprasad, T. P. N. (2021). In silico analysis of a potential antidiabetic phytochemical erythrin against therapeutic targets of diabetes. *In Silico Pharmacology*, 9(1).
<https://doi.org/10.1007/s40203-020-00065-8>
- Ren, L., Qin, X., Cao, X., Wang, L., Bai, F., Bai, G., & Shen, Y. (2011). Structural insight into substrate specificity of human intestinal maltase-glucoamylase. *Protein and Cell*, 2(10), 827–836.
<https://doi.org/10.1007/s13238-011-1105-3>
- Sanmuga Priya, E., & Senthamil Selvan, P. (2017). Water hyacinth (*Eichhornia crassipes*) – An efficient and economic adsorbent for textile effluent treatment – A review. *Arabian Journal of Chemistry*, 10, S3548–S3558.
<https://doi.org/10.1016/j.arabjc.2014.03.002>
- Schrödinger, L. (2025). *The PyMOL Molecular Graphics System, Version 3.1.6.1*. Schrödinger, LLC. Retrieved from <http://www.pymol.org/>
- Shamsian, S., Sokouti, B., & Dastmalchi, S. (2024). Benchmarking different docking protocols for predicting the binding poses of ligands complexed with cyclooxygenase enzymes and screening chemical libraries. *BioImpacts*, 14.
<https://doi.org/10.34172/bi.2023.29955>
- Soliman, E. S., Hassan, R. A., & Farid, D. S. (2023). *Eichhornia crassipes* from wastes to valuable products in water purification and influence on growth and impregnability in overwhelmed broiler chickens. *Open Veterinary Journal*, 13(4), 451–465.
<https://doi.org/10.5455/OVJ.2023.v13.i4.7>
- Zetta, D. N., Setiyabudi, L., Issusilaningtyas, E., Indratmoko, S., & Aji, A. P. (2025). Potential Analysis of Herbal Active Compounds as Immunotherapeutic Agents against CLTA-4Receptor through in silico. *Jurnal Farmasi Sains Dan Praktis (JFSP)*, 11(1), 1–10.
<https://doi.org/10.31603/pharmacy.v11i1.9839>