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Article

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Evaluation of the Antidiabetic Potential of Selected Bioactive Compounds from Yam Bean (Pachyrhizus erosus): A preliminary in silico study

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Abstract

Diabetes mellitus is one of the most significant global public health challenges, with a steadily increasing prevalence, particularly in low- and middle-income countries. Despite the availability of several therapeutic options, their limitations and adverse effects underscore the urgent need for the discovery of novel antidiabetic agents. Natural products remain a valuable source of bioactive compounds with considerable potential for drug development. This study aimed to evaluate the antidiabetic potential of seven bioactive compounds isolated from yam bean (*Pachyrhizus erosus*) using an *in silico* approach combining physicochemical characterization, pharmacokinetic and toxicological profiling, and molecular docking analysis. The selected compounds, dolineone, daidzin, daidzein, genistein, gentisic acid, neodulin, and erosone were initially assessed for their physicochemical properties and drug-likeness using SwissADME. Their pharmacokinetic and toxicity profiles (ADMET) were subsequently predicted using pkCSM and ADMETlab 2.0. Molecular docking simulations were then performed against α-glucosidase (PDB ID: 3W37), a key therapeutic target involved in carbohydrate digestion and postprandial glucose regulation. The results demonstrated that most of the investigated compounds possessed physicochemical properties consistent with good oral bioavailability and exhibited favorable pharmacokinetic profiles. Toxicological predictions indicated a low risk of toxicity, including the absence of predicted hepatotoxicity for all compounds. Molecular docking analysis showed that all seven compounds interacted with the active site of α-glucosidase. Among them, daidzin exhibited the strongest binding affinity (−8.3 kcal/mol), surpassing that of the reference inhibitor acarbose (−8.0 kcal/mol). Furthermore, daidzin formed multiple interactions with key catalytic amino acid residues, suggesting a high inhibitory potential against α-glucosidase. Overall, these findings highlight the potential of bioactive compounds from *Pachyrhizus erosus*, particularly daidzin, as promising candidates for the development of novel α-glucosidase inhibitors for diabetes management. However, further *in vitro* and *in vivo* studies are warranted to validate their biological activity, elucidate their mechanisms of action, and assess their therapeutic efficacy and safety.

Keywords:
Diabetes mellitus; *Pachyrhizus erosus*; α-glucosidase; virtual screening; bioactive compounds.

Résumé

Le diabète sucré constitue l'un des plus grands défis de santé publique à l'échelle mondiale, avec une prévalence en constante augmentation, particulièrement dans les pays à revenu faible et intermédiaire. Malgré la disponibilité de plusieurs options thérapeutiques, leurs limites et leurs effets indésirables soulignent la nécessité urgente de découvrir de nouveaux agents antidiabétiques. Les produits naturels demeurent une source précieuse de composés bioactifs présentant un fort potentiel pour le développement de nouveaux médicaments. La présente étude avait pour objectif d'évaluer le potentiel antidiabétique de sept composés bioactifs isolés du haricot igname (*Pachyrhizus erosus*) à l'aide d'une approche *in silico* combinant la caractérisation physicochimique, l'évaluation des profils pharmacocinétiques et toxicologiques ainsi que l'analyse par docking moléculaire. Les composés sélectionnés, à savoir la dolinéone, la daidzine, la daidzéine, la génistéine, l'acide gentisique, la néoduline et l'érosone, ont d'abord été évalués pour leurs propriétés physicochimiques et leur conformité aux critères de « drug-likeness » à l'aide de SwissADME. Leurs profils pharmacocinétiques et toxicologiques (ADMET) ont ensuite été prédits à l'aide de pkCSM et d'ADMETlab 2.0. Enfin, des simulations de docking moléculaire ont été réalisées contre l'α-glucosidase (PDB ID : 3W37), une cible thérapeutique clé impliquée dans la digestion des glucides et la régulation de la glycémie postprandiale. Les résultats ont montré que la majorité des composés étudiés possédaient des propriétés physicochimiques compatibles avec une bonne biodisponibilité orale et présentaient des profils pharmacocinétiques favorables. Les prédictions toxicologiques ont révélé un faible risque de toxicité, notamment l'absence d'hépatotoxicité prédite pour l'ensemble des composés. L'analyse par docking moléculaire a montré que les sept composés interagissaient avec le site actif de l'α-glucosidase. Parmi eux, la daidzine a présenté la plus forte affinité de liaison (−8,3 kcal/mol), surpassant celle de l'inhibiteur de référence, l'acarbose (−8,0 kcal/mol). En outre, la daidzine a établi de multiples interactions avec des résidus catalytiques clés, suggérant un fort potentiel inhibiteur vis-à-vis de l'α-glucosidase. Dans l'ensemble, ces résultats mettent en évidence le potentiel des composés bioactifs de *Pachyrhizus erosus*, en particulier de la daidzine, en tant que candidats prometteurs pour le développement de nouveaux inhibiteurs de l'α-glucosidase destinés à la prise en charge du diabète. Toutefois, des études complémentaires *in vitro* et *in vivo* sont nécessaires afin de confirmer leur activité biologique, d'élucider leurs mécanismes d'action et d'évaluer leur efficacité thérapeutique ainsi que leur innocuité.

Mots-clés:
Diabète sucré ; *Pachyrhizus erosus* ; α-glucosidase ; criblage virtuel ; composés bioactifs.

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1. Introduction

Diabetes mellitus is one of the most pressing global public health challenges, affecting hundreds of millions of people worldwide. It is among the oldest diseases known to humankind, yet its prevalence continues to rise at an alarming rate, reaching epidemic proportions. Diabetes is a chronic metabolic disorder characterized by persistent hyperglycemia resulting either from insufficient insulin secretion by the pancreas or from the body's inability to effectively utilize insulin, the hormone responsible for regulating blood glucose levels (Proença et al., 2017; Liu et al., 2021).

According to the 11th edition of the International Diabetes Federation (IDF) Diabetes Atlas, 11.1% of the global adult population (20-79 years) lives with diabetes, equating to 589 million people. Over 4 in 10 individuals with the condition remain undiagnosed. By 2050, cases are projected to surge by 46% to 853 million (IDF, 2025).

Contrary to common misconceptions, diabetes is no longer confined to developed nations. The disease has become increasingly prevalent in developing regions, particularly in Africa, where limited access to healthcare services and delayed diagnosis substantially worsen disease outcomes. Nearly 90% of individuals with undiagnosed diabetes reside in low- and middle-income countries, while more than half of diabetes cases in Africa, Southeast Asia, and the Western Pacific remain undiagnosed (IDF, 2025). This situation is further exacerbated by significant inequalities in access to appropriate therapeutic interventions.

Current diabetes management relies on lifestyle modifications, including dietary control and regular physical activity, together with pharmacological therapies such as insulin and oral hypoglycemic agents (Oser et al, 2025). Although these treatments have significantly improved disease management, they remain associated with several limitations, including adverse effects, high treatment costs, and reduced accessibility in resource-limited settings. Consequently, the discovery of novel, safe, effective, and affordable antidiabetic agents remain a major research priority.

Natural products have historically served as an invaluable source of therapeutic agents. Africa possesses an exceptionally rich biodiversity containing numerous medicinal plants with demonstrated pharmacological activities, including antidiabetic properties (Holaly et al., 2015). Several studies have reported that African medicinal plants constitute promising sources of bioactive compounds capable of improving glycemic control and contributing to diabetes management (Karou et al., 2011; Tshibangu et al., 2024). Among these medicinal resources, yam bean (*Pachyrhizus erosus*), commonly known as jicama, is a tuberous legume widely cultivated and consumed in many tropical and subtropical regions (Figure 1). Besides its recognized nutritional value, *P. erosus* contains a diverse array of bioactive phytochemicals exhibiting antioxidant, anti-inflammatory, and potential antidiabetic activities (Reddy, 2015).

Figure 1. Yam bean plant (left) and tubers (right). (Reddy, 2015).

Although *Pachyrhizus erosus* is native to Central America, it has been successfully introduced into several tropical regions, including Africa, where it is cultivated on a limited scale for its edible tubers and medicinal potential (Ma et al, 2018). In rural communities of the Democratic Republic of the Congo, the tuber of *Fabaceae* species is traditionally consumed and is reputed for its beneficial effects in the management of diabetes.

In this context, the present study aimed to evaluate the antidiabetic potential of selected bioactive compounds isolated from *Pachyrhizus erosus* through an *in-silico* approach. Specifically, the study investigated the physicochemical characteristics, drug-likeness, pharmacokinetic and toxicological properties (ADMET), and molecular interactions of these compounds with α-glucosidase, a key enzyme involved in carbohydrate digestion (Hasimun and Adnyana, 2019). α-Glucosidase catalyzes the hydrolysis of oligosaccharides and disaccharides into absorbable monosaccharides in the small intestine, thereby playing a crucial role in postprandial glucose regulation (Proença et al., 2017; Liu et al., 2021). Consequently, inhibition of this enzyme represents a well-established therapeutic strategy for the management of type 2 diabetes mellitus.

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By combining physicochemical characterization, ADMET prediction, and molecular docking analyses, this work seeks to identify promising natural α-glucosidase inhibitors while contributing to the scientific valorization of the rich biodiversity of the Democratic Republic of the Congo. The selected compounds are predominantly found in the tubers of *P. erosus* (Reddy, 2015). Previous studies have demonstrated that the antidiabetic properties of this plant are primarily attributed to its tubers, making them a valuable source of bioactive compounds with potential therapeutic applications (Jaiswal et al., 2022; Lu et al., 2008).

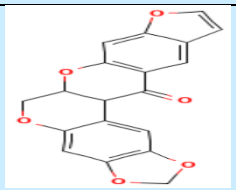
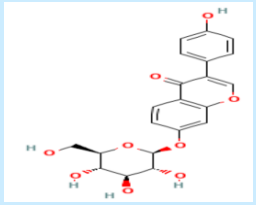
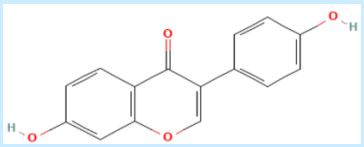
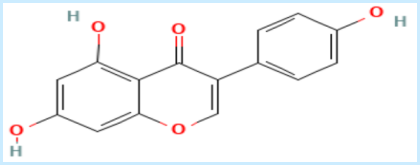
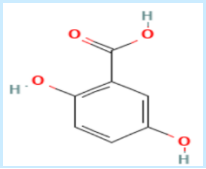
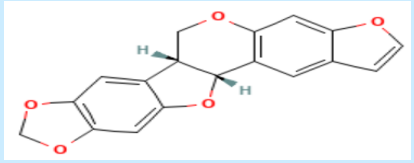
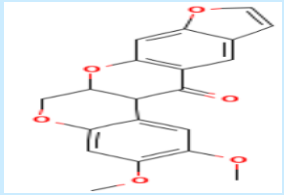
The findings may provide a theoretical basis for the future development of plant-derived antidiabetic agents and support subsequent experimental investigations.

2. Materials and Methods

2.1. Section of bioactive compounds

Seven bioactive compounds isolated from *Pachyrhizus erosus* were selected for this study (Table 1): dolineone, daidzin, daidzein, genistein, gentisic acid, neodulin, and erosone. These compounds were chosen based on their reported phytochemical relevance and their potential antidiabetic properties described in the literature (Jaiswal et al., 2022; Lu et al., 2008).

Table 1. Structure, PubChem CID and chemical class of the investigated phytochemicals

Compound	Chemical structure	PubChem CID	Chemical class
Dolineone		5316959	Rotenoid
Daidzin		107971	Glycosylated isoflavone
Daidzein		5281708	Isoflavone
Genistein		5280961	Isoflavone
Gentisic acid		3469	Phenolic acid
Neodulin		337776	Rotenoid
Erosone		5317190	Rotenoid

2.2. Ligand and receptor preparation

The phytochemicals identified from *P.erosus* were retrieved from the PubChem database using their respective PubChem CIDs. Energy minimization was performed using PM6 force field.

The three-dimensional structure of α-glucosidase (PDB ID: 3W37) was retrieved from the Protein Data Bank (PDB). Prior to molecular docking, the co-crystallized ligand (acarbose) and crystallographic water molecules were removed, and all missing hydrogen atoms were added to prepare the receptor for docking calculations. Molecular docking simulations were performed using AutoDock Vina, as implemented in the PyRx platform.

2.3. Drug-Likeness and Physicochemical Property Analysis

Drug-likeness and physicochemical properties of the selected compounds were evaluated using the SwissADME web server (Daina et al., 2017).

The obtained physicochemical parameters were subsequently analyzed to identify compounds exhibiting favorable characteristics for oral drug development according to Lipinski's criteria (Lipinski, 2000).

2.4. ADMET Prediction

The pharmacokinetic and toxicological profiles of the selected compounds were predicted using the pkCSM (Pires et al., 2015) and ADMETlab 2.0 (Xiong et al., 2021) web servers.

For each prediction platform, the canonical SMILES representation of every compound was used as the input structure.

The predicted ADMET profiles were interpreted to identify compounds exhibiting favorable pharmacokinetic behavior together with acceptable safety characteristics.

2.5. Molecular Docking

Molecular docking simulations were performed using AutoDock Vina implemented in the PyRx platform to investigate the binding interactions between the selected phytochemicals and α-glucosidase. Binding affinity values (kcal/mol) were used to estimate the stability of each ligand–protein complex, whereas interaction analyses allowed the identification of key amino acid residues involved in molecular recognition and inhibition.

3. Résultats

3.1. Physicochemical Properties

The canonical SMILES codes were subsequently submitted to the computational platforms employed in this study to predict the physicochemical properties of the selected compounds. These parameters play a fundamental role in medicinal chemistry because they largely determine the intrinsic chemical behavior, oral bioavailability, membrane permeability, and overall drug-likeness of candidate molecules.

The investigated descriptors included molecular weight (MW), octanol/water partition coefficient (LogP), number of hydrogen bond acceptors (HBA), number of hydrogen bond donors (HBD), number of rotatable bonds (nRot), number of rigid bonds (nRig), molecular flexibility (Flexibility = nRot/nRig), molar refractivity (MR), and topological polar surface area (TPSA). Physicochemical parameters (Table 2) were predicted using ADMETlab 2.0, whereas molar refractivity values were obtained from SwissADME.**:**

Table 2. Physicochemical parameters of ligands

Compounds	Formula	MW	Log P	nHA	nHD	nRot	nRig	Fx	MR	TPSA
Dolineone	$C_{19}H_{12}O_6$	336.30	4.057	6	0	0	6	0 .000	85.71	67.13
Daidzin	$C_{21}H_{20}O_9$	416.38	0.344	9	5	4	4	0.167	104.09	149.82
Daidzein	$C_{15}H_{10}O_4$	254.24	2.871	4	2	1	3	0.057	71.97	70.67
Genistein	$C_{21}H_{20}O_{10}$	432.38	0.049	10	6	4	4	0.167	106.11	170.05
Gentisic acid	$C_9H_{13}NO_5$	215.21	0.266	6	6	2	1	0.286	53.04	124.01
Neodulin	$C_{18}H_{12}O_5$	308.28	3.278	5	0	0	6	0.000	80.49	50.06
Erosone	$C_{20}H_{16}O_6$	352.34	3.569	6	0	2	5	0.077	92.64	67.13

As summarized in Table 2, the molecular weights of the investigated compounds ranged from 215.21 to 432.38 g/mol, remaining well below the 500 g/mol threshold recommended by Lipinski's Rule of Five. Likewise, all compounds exhibited LogP values below 5, suggesting favorable lipophilicity for oral administration.

The number of hydrogen bond acceptors varied between 4 and 10, satisfying Lipinski's criterion for all compounds. Similarly, most compounds complied with the hydrogen bond donor requirement (≤ 5), with the exception of genistein (compound 4) and gentisic acid (compound 5), which slightly exceeded this limit.

Hydrogen bonding represents one of the principal non-covalent interactions governing ligand–protein recognition and stabilization, together with van der Waals interactions and aromatic π–π stacking interactions (Tunga et al., 2020). Therefore, compounds possessing a greater number of hydrogen bond donors and acceptors are generally expected to establish stronger interactions within protein binding pockets (Matondo et al, 2018). Based on the total number of hydrogen-bonding sites, compound 4 exhibited the highest hydrogen-bonding capacity, followed by compounds 2, 5, 1, 3, 7, and 6.

Hydrophobic interactions were evaluated through the LogP descriptor, which reflects molecular lipophilicity and indirectly estimates the contribution of van der Waals interactions during ligand binding. According to the predicted LogP values, compounds 1 and 7 displayed the highest lipophilic character, followed by compounds 6, 3, 2, 5, and 4.

Molecular flexibility is another important determinant of biological activity because flexible molecules can better adapt to the geometry of receptor binding pockets. Based on the calculated flexibility index, compounds 5, 2, and 4 were identified as the most flexible molecules within the investigated dataset, whereas compounds 1 and 6 exhibited the lowest flexibility.

Molar refractivity is an important physicochemical descriptor associated with molecular polarizability, London dispersion forces, receptor affinity, cellular uptake, and bioavailability. Recommended values generally range between 40 and 130 cm^3/mol (Cerqueira et al., 2015). All investigated compounds fell within this optimal interval, suggesting an appropriate capacity to establish favorable dispersion interactions with biological targets.

Finally, the predicted TPSA values ranged between 50 and 124 $Å^2$ for most compounds, remaining within the recommended range (20-140 $Å^2$) associated with satisfactory intestinal absorption and membrane permeability. Only compounds 2 and 4 exhibited slightly higher TPSA values, which may negatively influence passive membrane diffusion despite their favorable hydrogen-bonding capabilities.

Overall, the physicochemical analysis indicates that most of the selected phytochemicals possess molecular characteristics compatible with orally active drug candidates and therefore warrant further pharmacokinetic and molecular docking investigations.

3.2. Pharmacokinetic and toxicological properties

Early evaluation of pharmacokinetic and toxicological properties has become an essential step in modern drug discovery, as unfavorable ADMET characteristics remain one of the leading causes of failure during drug development (Mvondo et al, 2021; Young, 2009). Besides exhibiting high affinity toward a therapeutic target, an ideal drug candidate should possess favorable absorption, appropriate tissue distribution, acceptable metabolic stability, efficient elimination, and minimal toxicity. Therefore, the ADMET profiles of the seven selected phytochemicals were predicted using the pkCSM and ADMETlab 2.0 platforms. The predicted parameters are summarized in Table 3.

Table 3. Pharmacokinetic and toxicological properties of ligands

Parameters	Ligand 1	Ligand 2	Ligand 3	Ligand 4	Ligand 5	Ligand 6	Ligand 7
Absorption & distribution							
BBB	-0.376	-1.232	-0.064	-1.417	-0.863	-0.095	-0.330
IAH (%)	99.88	51.32	94.84	35.51	44.13	99.87	98.77
Biodisponibility Score	0.55	0.55	0.55	0.55	0.55	0.55	0.55
Metabolism							
CY2D6	Non	Non	Non	Non	Non	Non	Non
CYP3A4	Oui	Non	Non	Non	Non	Non	Oui
Excretion							
Total Clearance (log mL/min/kg)	0.319	0.104	0.164	0.096	0.302	0.264	0.455
Renal substrat OCT2	Non	Non	Non	Non	Non	Non	Non
Toxicity							
Ames Test	Oui	Non	Non	Non	Non	Oui	Oui
Hepatotoxicity	Non	Non	Non	Non	Non	Non	Non
Acute oral toxicity (LD50 in mol /Kg and mg/Kg)	3.013	2,735	2,164	2.643	2.484	2.816	2.834

- **Absorption and Distribution**

Human intestinal absorption (HIA) is a key determinant of oral bioavailability. As shown in Table 3, compounds 1 (dolineone), 3 (daidzein), 6 (neoduline), and 7 (erosone)

exhibited excellent predicted intestinal absorption, with HIA values exceeding 94%. In contrast, compounds 4 (genistein) and 5 (gentisic acid) showed comparatively lower absorption rates (35.51% and 44.13%, respectively), suggesting a less favorable oral absorption profile.

The permeability of compounds across the blood–brain barrier (BBB) is another important pharmacokinetic parameter. For antidiabetic agents targeting peripheral tissues, limited BBB penetration is generally considered advantageous because it minimizes the risk of central nervous system adverse effects. All investigated compounds exhibited negative LogBB values, indicating poor BBB permeability. Consequently, these molecules are unlikely to accumulate in the brain and are therefore expected to present a low risk of central neurotoxicity.

Interestingly, all compounds showed an identical bioavailability score of 0.55, suggesting satisfactory oral bioavailability and supporting their potential as orally administered drug candidates (Martin, 2005).

- **Metabolism**

Drug metabolism is largely mediated by hepatic cytochrome P450 enzymes, particularly CYP2D6 and CYP3A4, which are responsible for the biotransformation of a substantial proportion of clinically approved drugs.

The computational predictions revealed that none of the investigated compounds inhibited CYP2D6, indicating a low probability of metabolic interactions involving this enzyme. Likewise, most compounds were predicted to be non-inhibitors of CYP3A4, except dolineone (compound 1) and erosone (compound 7), which may interfere with CYP3A4-mediated metabolism. This observation should be considered during future pharmacological investigations because CYP3A4 inhibition may contribute to clinically relevant drug–drug interactions.

- **Excretion**

Total clearance predictions indicated moderate elimination rates for all investigated compounds, while none were predicted to be substrates of the renal organic cation transporter OCT2. These findings suggest that renal transporter-mediated elimination is unlikely to play a major role in the clearance of these phytochemicals.

- **Toxicological Profile**

The predicted toxicological properties were generally encouraging. None of the investigated compounds exhibited hepatotoxicity, an important finding considering that hepatic metabolism is the primary route of drug biotransformation.

Regarding mutagenicity, the Ames test predicted that compounds 1, 6, and 7 may possess mutagenic potential, whereas compounds 2, 3, 4, and 5 were predicted to be non-mutagenic. Consequently, additional experimental toxicological evaluations will be required before considering the former compounds for pharmaceutical development.

Acute oral toxicity predictions (LD_{50}) classified all investigated compounds within GHS Toxicity Category IV, indicating slight acute toxicity after oral administration. Overall, these findings suggest an acceptable preliminary safety profile for the majority of the evaluated phytochemicals.

Collectively, the ADMET analysis demonstrated that most bioactive compounds from Pachyrhizus erosus possess favorable pharmacokinetic characteristics, including satisfactory intestinal absorption, acceptable oral bioavailability, limited BBB permeability, and the absence of hepatotoxicity. Among the investigated molecules, daidzin exhibited one of the most balanced pharmacokinetic profiles, further supporting its potential as a promising antidiabetic lead compound. Nevertheless, additional in vitro and in vivo pharmacokinetic and toxicological studies are required to validate these computational predictions.

3.3. Molecular docking analysis

Molecular docking simulations were performed to investigate the binding affinity and interaction patterns of the selected phytochemicals toward the catalytic site of α-glucosidase (PDB ID: 3W37). The native co-crystallized inhibitor, acarbose, was used as the reference compound to assess the inhibitory potential of the investigated molecules (Chiasson, 2022). The calculated binding affinities are presented in Table 4.

Table 4. Binding affinity in kcal/mol of ligands and α-glucosidase complexes

Complex	Binding affinity
3W37_native ligand	-8.0
3W37_Ligand 1	-8.0
3W37_Ligand 2	-8.3
3W37_Ligand 3	-6.9
3W37_Ligand 4	-7.9
3W37_Ligand 5	-5.9
3W37_Ligand 6	-7.8
3W37_Ligand 7	-7.3

All seven bioactive compounds exhibited negative binding

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free energies (ΔG), indicating spontaneous binding and the formation of thermodynamically stable ligand–protein complexes. In molecular docking studies, more negative binding affinity values generally reflect stronger ligand–receptor interactions and a higher probability of inhibitory activity.

Among the investigated compounds, daidzin (compound 2) exhibited the strongest binding affinity toward α-glucosidase (−8.3 kcal/mol), surpassing that of the reference inhibitor acarbose (−8.0 kcal/mol). This finding suggests that daidzin has a greater potential to interact with the enzyme's catalytic pocket, highlighting it as the most promising α-glucosidase inhibitor identified in this study.

Dolineone (compound 1) exhibited a binding affinity identical to that of acarbose (-8.0 kcal/mol), whereas genistein (compound 4) and neoduline (compound 6) produced comparable docking scores of -7.9 and -7.8 kcal/mol, respectively. In contrast, daidzein (compound 3), erosone (compound 7), and gentisic acid (compound 5) showed lower binding affinities, suggesting comparatively weaker interactions with the target enzyme.

Overall, the ranking of binding affinities was as follows: Daidzin > Dolineone ≈ Acarbose > Genistein > Neoduline > Erosone > Daidzein > Gentisic acid. These findings indicate that most compounds possess appreciable affinity toward α-glucosidase, with daidzin emerging as the most promising lead compound.

3.4. Binding mode of the reference ligand (acarbose)

To establish a reliable reference for the molecular docking analysis, the interaction pattern of the co-crystallized ligand, acarbose, with α-glucosidase was first examined. As a clinically approved α-glucosidase inhibitor, acarbose provides an appropriate benchmark for evaluating the binding behavior of the investigated phytochemicals.

The catalytic residues involved in acarbose binding include Asp518, Trp516, and Met519, confirming that the ligand occupies the catalytic pocket of the enzyme. In addition to these key interactions, acarbose forms an extensive interaction network with several amino acid residues, including Phe649, Trp516, Trp376, Ile441, Leu405, Ser676, Arg672, Asp518, Trp613, Tyr292, Trp481, Met519, Arg281, Ala555, Leu283, Ala284, and Phe525 through van der Waals contacts.

Furthermore, the reference ligand establishes four conventional hydrogen bonds with Asp404, His674, Asp616, and Asp282. Additional hydrogen-bond interactions with crystallographic water molecules contribute to further stabilization of the ligand–protein complex. The interaction profile of acarbose highlights the importance of hydrogen bonding and hydrophobic contacts in maintaining stable binding within the catalytic cavity of α-glucosidase. This binding pattern serves as a structural reference for comparing the interaction modes of the bioactive compounds evaluated in the present study.

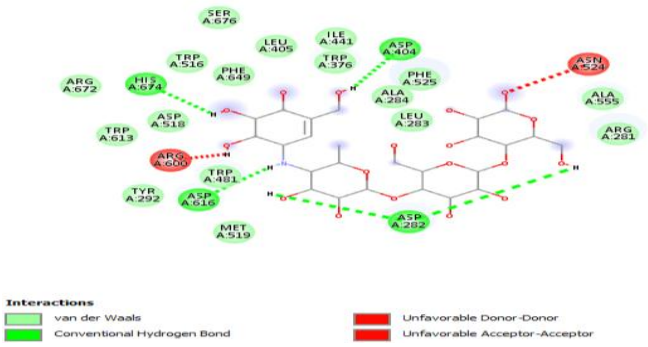
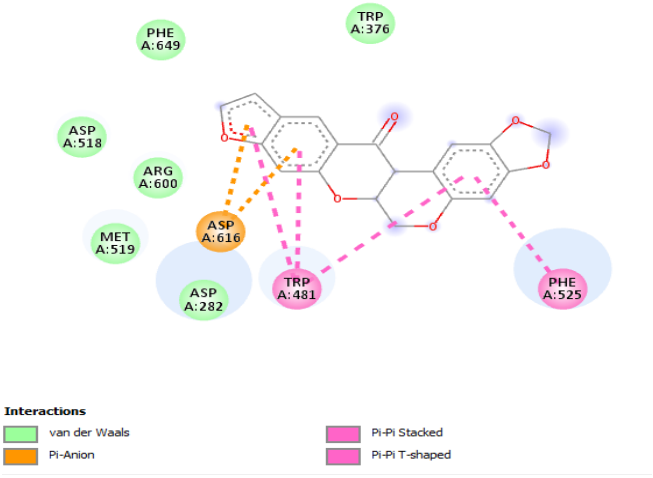


Figure 2. 2D representation of the interaction between native ligand and receptor.

- **Ligand-Protein interactions analysis**

Binding affinity alone is insufficient to accurately predict inhibitory activity. The nature, strength, and spatial distribution of ligand–protein interactions within the catalytic pocket are equally critical for understanding molecular recognition and the mechanisms underlying enzyme inhibition.



Ligand 1_3W37

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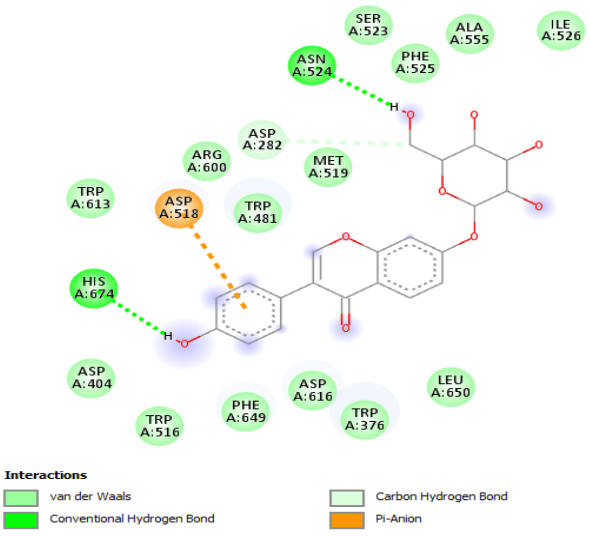

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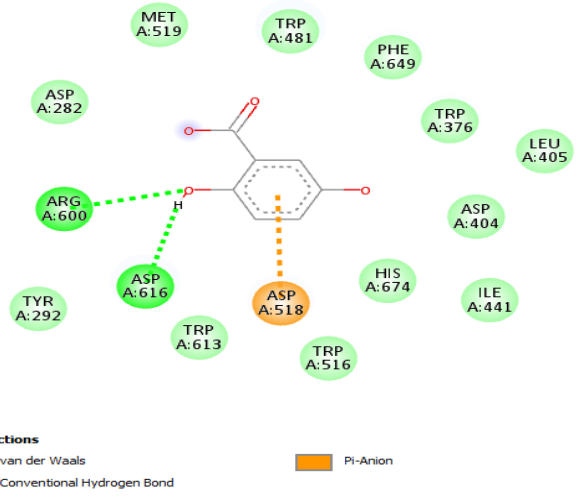

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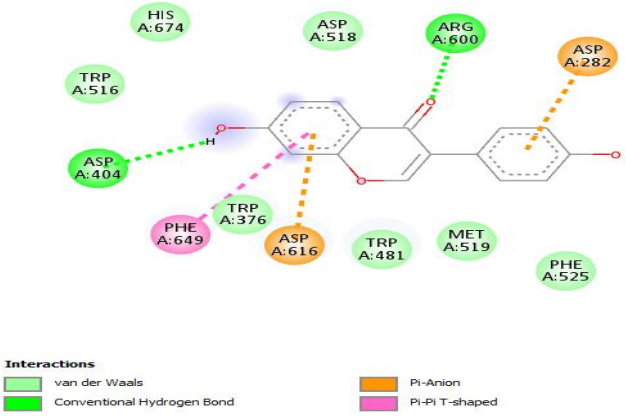

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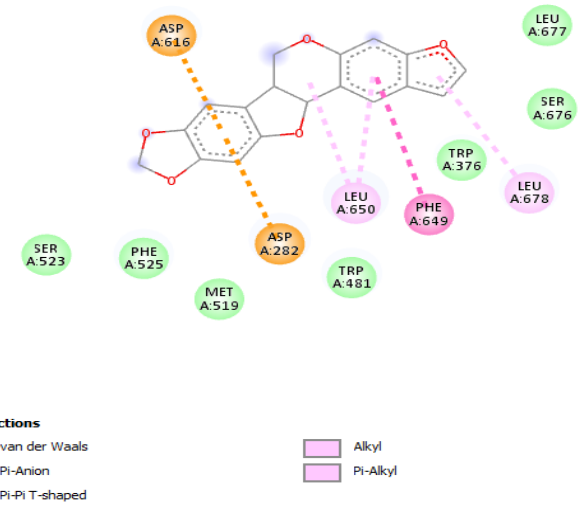

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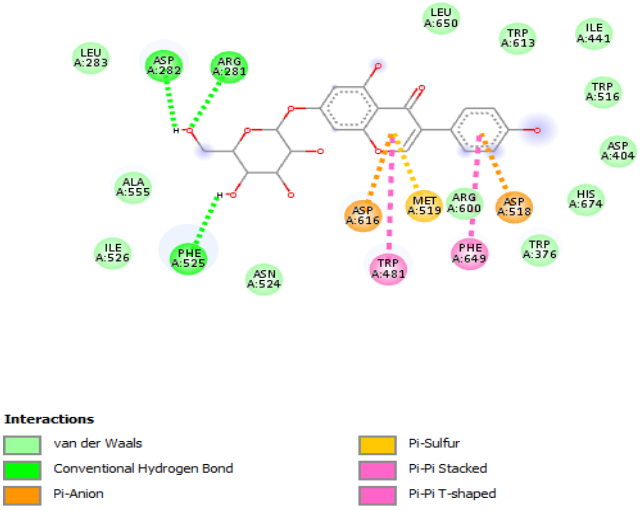

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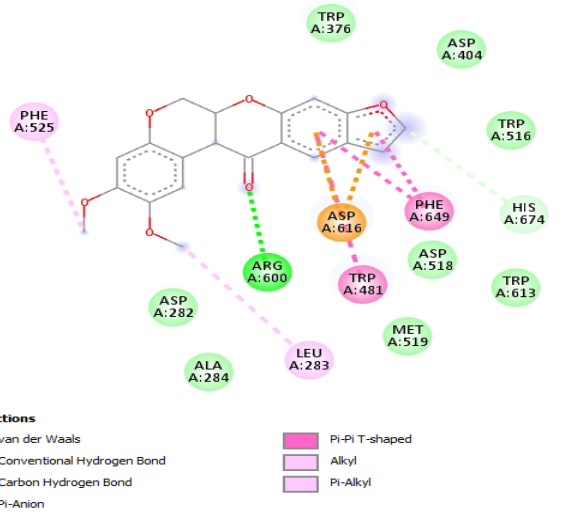

Ligand 7_3W37

Figure 3. 2D representation of the interactions in ligand-receptor complexes

The interaction diagrams (Figure 3) revealed that all investigated compounds established multiple non-covalent interactions with α-glucosidase, including conventional hydrogen bonds, van der Waals interactions, π-π stacking, π-π T-shaped interactions, π-alkyl interactions, and π-anion interactions.

Particular attention was paid to the catalytic amino acid residues Asp518, Trp516, Met519, and Asn520, which are directly involved in the enzymatic mechanism of α-glucosidase. Remarkably, all investigated ligands interacted with at least one of these catalytically important residues, supporting their potential inhibitory activity.

Among these residues, Trp516, Asp518, and Met519 appeared to play central roles in ligand stabilization, being repeatedly involved in the binding of the highest-scoring compounds.

Daidzin−α-glucosidase complex (Ligand 2_3W37)

Daidzin exhibited the most favorable docking profile among all investigated compounds. The ligand established direct interactions with the catalytic residues Asp518, Trp516, and Met519, demonstrating excellent complementarity with the enzyme active site.

In addition, the complex was stabilized by two strong conventional hydrogen bonds involving Asn524 and His674, together with several van der Waals interactions and a π-anion interaction. The combination of these attractive non-covalent forces is expected to enhance the stability of the ligand-protein complex and may explain the superior binding affinity observed for daidzin (Mulongo et al, 2025).

Dolineone−α-glucosidase Complex (Ligand 1_3W37)

Dolineone exhibited a binding affinity equivalent to that of acarbose. The ligand interacted directly with the catalytic residue Met519 and established several van der Waals interactions involving Trp376, Phe649, Asp518, Arg600, and Asp282.

Furthermore, aromatic π-π stacking and π-π T-shaped interactions involving Trp481 and Phe525, together with a π-anion interaction with Asp616, substantially contributed to complex stabilization. These aromatic interactions are known to play an important role in strengthening ligand binding through London dispersion forces.

Genistein−α-Glucosidase Complex (Ligand 4_3W37)

Genistein displayed a favorable docking score and formed a stable binding network within the catalytic cavity. Besides multiple aromatic π-interactions, the ligand established three conventional hydrogen bonds with Asp282, Arg281, and Phe525. The coexistence of hydrogen bonding and aromatic interactions is likely responsible for the good thermodynamic stability predicted for this complex.

Neoduline−α-glucosidase Complex

Although neoduline did not establish conventional hydrogen bonds with catalytic residues, its complex remained highly stable owing to the presence of multiple aromatic interactions, including π-anion, π-alkyl, and π-π T-shaped interactions. This observation highlights that strong binding is not exclusively governed by hydrogen bonds. Aromatic and hydrophobic interactions may also provide substantial contributions to ligand stabilization within enzyme active sites (Kasende et al, 2017; Matondo et al 2022; Ashande et al, 2022).

Taken together, the molecular docking results indicate that the investigated phytochemicals are capable of effectively occupying the catalytic cavity of α-glucosidase. Their inhibitory potential appears to arise from a synergistic combination of hydrogen bonding, hydrophobic contacts, aromatic π-interactions, and electrostatic interactions.

Among all evaluated compounds, daidzin consistently exhibited the most favorable binding affinity together with the most relevant interaction profile involving catalytic amino acid residues. These findings strongly suggest that daidzin represents the most promising natural α-glucosidase inhibitor identified in the present computational investigation and deserves further validation through in vitro, in vivo, and molecular dynamics studies.

4. Conclusion

The present study employed an *in silico strategy* to investigate the antidiabetic potential of seven bioactive compounds isolated from *Pachyrhizus erosus*. By combining physicochemical characterization, drug-likeness evaluation, ADMET prediction, and molecular docking analyses, this work provides a comprehensive preliminary assessment of the therapeutic potential of these natural products as α-glucosidase inhibitors.

The physicochemical analysis demonstrated that most of the investigated compounds comply with the fundamental criteria

for orally active drug candidates, exhibiting favorable molecular weight, lipophilicity, hydrogen-bonding capacity, and topological polar surface area. In addition, the predicted pharmacokinetic profiles suggested satisfactory intestinal absorption, acceptable oral bioavailability, limited blood-brain barrier permeability, and the absence of hepatotoxicity for all compounds, although several molecules require further toxicological evaluation because of their predicted mutagenic potential.

Molecular docking simulations confirmed that all selected phytochemicals are capable of interacting with the catalytic pocket of α-glucosidase through multiple non-covalent interactions, including hydrogen bonds, van der Waals contacts, and aromatic π-interactions. Among the investigated compounds, daidzin exhibited the strongest binding affinity (-8.3 kcal/mol), surpassing the reference inhibitor acarbose (-8.0 kcal/mol). Furthermore, daidzin established stable interactions with key catalytic residues, including Asp518, Trp516, and Met519, suggesting a high potential to inhibit α-glucosidase activity.

Overall, these findings identify daidzin as the most promising lead compound among the phytochemicals investigated and highlight Pachyrhizus erosus as a valuable source of natural molecules with potential applications in the management of type 2 diabetes mellitus.

Nevertheless, the present study is based exclusively on computational predictions. Therefore, additional in vitro enzymatic assays, in vivo pharmacological studies, and molecular dynamics simulations are required to validate the predicted binding modes, evaluate the biological activity of the identified compounds, and further investigate their pharmacological and toxicological profiles.

In conclusion, this work contributes to the growing body of evidence supporting the therapeutic potential of natural products in antidiabetic drug discovery. The computational framework presented herein may also facilitate the identification and optimization of novel plant-derived α-glucosidase inhibitors for the development of safer and more effective antidiabetic therapies.

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