

Alpha-glucosidase inhibitory activities of furanoflavonoids isolated from *Pongamia pinnata*: DFT calculation, molecular modelling and *in vitro* studies

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Abstract

Objective: This study focuses on evaluating the inhibitory activity of pongaglabrone and pongapin, isolated from *Pongamia pinnata* in our previous research, inhibit α -glucosidase, an enzyme involved in carbohydrate metabolism. Inhibition of α -glucosidase is a key target for controlling type 2 diabetes, making these compounds promising candidates for further research. **Methods:** *In vitro* inhibitory activity assays were conducted to evaluate the effects of pongaglabrone and pongapin on α -glucosidase. Computational approaches, including Density Functional Theory (DFT) calculations, molecular docking, and molecular dynamics simulations, were employed to assess molecular interactions and stability. The absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of these compounds were also predicted. **Results:** Pongapin and pongaglabrone demonstrated inhibitory activity on α -glucosidase, with IC_{50} values of 116.5 ± 5.02 μ g/mL and 137.10 ± 14.67 μ g/mL, respectively. Molecular docking revealed binding affinities of 7.564 kcal/mol for pongapin and 7.929 kcal/mol for pongaglabrone. Molecular dynamic simulations confirmed that the complexes between the two compounds and α -glucosidase remained stable over a 200 ns simulation period, indicating favorable interactions and potential inhibitory activity. ADMET analysis suggested that while both compounds are absorbable via the digestive tract, they may present toxicity risks. **Conclusion:** Pongaglabrone and pongapin, based on *in vitro* and *in silico* evaluations, demonstrate potential as anti- α -glucosidase agents.

Keywords

Pongamia pinnata, pongaglabrone, pongapin, anti- α -glucosidase, DFT

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Introduction

Diabetes is an endocrine metabolic disorder characterized by abnormal levels of glucose in the bloodstream.¹ The world's total number of diabetes cases is expected to reach 578 million by 2030 caused by inadequate lifestyle choices. As a result, diabetes is becoming more common worldwide.² Until now, no conclusive therapy has been developed to manage the metabolic abnormalities attributed to diabetes successfully. A non-invasive approach that is beneficial in managing hyperglycemia linked to type-2 diabetes involves focusing on α -glucosidase, enzymes that catalyze the breakdown of starch in the intestines.³ Alpha glucosidase, also known as α -D-glucoside glucohydrolase, are exoenzymes that hydrolyze terminal glycosidic bonds, therefore liberating α -glucose from the nonreducing end of the substrate molecule. These enzymes are found in large quantities in the tissues of plants, animals, and microbes. Due to their ability to catalyze both hydrolysis and transglucosylation, some α -glucosidases

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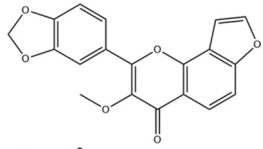
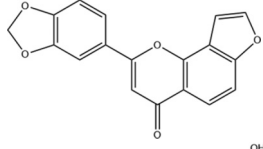
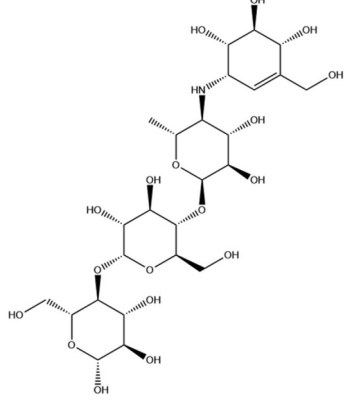
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Table 1. Anti- α -glucosidase activity.

Compound	Structure	% Inhibition		
		at 500 $\mu\text{g/mL}$	at 100 $\mu\text{g/mL}$	IC ₅₀ ($\mu\text{g/mL}$)
Pongapin		88.76 $\pm$ 2.16	55.89 $\pm$ 1.48	116.5 $\pm$ 5.02
Pongaglabrone		85.24 $\pm$ 6.45	44.39 $\pm$ 4.33	137.10 $\pm$ 14.67
Acarbose*		79.95 $\pm$ 7.06	44.24 $\pm$ 5.15	160.99 $\pm$ 14.3

*Positive control.

are sometimes referred to as transglucosidases.⁴ In individuals with diabetes, α -glucosidase breaks down carbs and raises postprandial glucose levels. Diabetes risk can be decreased by inhibiting the activity of these enzymes, which can also regulate postprandial hyperglycemia.⁵ The only recognized inhibitors of these enzymes at present are voglibose, miglitol, and acarbose. While these inhibitors decrease the absorption of glucose, they have unfavorable gastrointestinal side effects that make it difficult to use them. Thus, investments in research are still being made to discover new inhibitors that have better effectiveness and fewer negative side effects. Plant-based natural products have been demonstrated to be a viable source of medicinal compounds that have lower toxicity and negative effects.³

Pongamia pinnata (L.) Pierre belongs to the genus *Pongamia* (Fabaceae). According to reports, *Pongamia* is native to the Indian subcontinent and Southeast Asia. Traditional medicine has long utilized all parts of this plant to treat a wide range of illnesses and wounds.^{6–13} Numerous chemicals belonging to different classes were found as a consequence of the phytochemical research. The most frequently discovered chemicals from *P. pinnata* are flavonoid derivatives, including flavones, flavans, and chalcones.^{6,14–22} This species also included several additional class-specific chemicals, including sesquiterpene,²³ diterpene,²⁴ triterpene,^{21,23} steroids,²⁵ amino acid derivatives,^{26,27} disaccharide,²⁵ fatty acids,^{23,28} and esters.^{25,29} The pharmacological studies demonstrated that this plant revealed a wide range of biological activities, including the

antioxidant,^{14,18,30} antimicrobial,^{14,18,31,32} anti-parasite,^{33,34} anti-inflammatory,^{34–37} anti-convulsant,^{38–40} anti-diabetic,^{8,19,41–44} anti-hyperammonemic,⁴⁵ cytotoxicity,^{14,46} anthelmintic,^{47,48} insecticidal,^{49–54} and immunomodulatory activities.⁵⁵

In our previous publication, we successfully isolated pongaglabrone and pongapin from *Pongamia pinnata* and elucidated their structures using NMR and MS analyses.⁵⁶ Besides, these furanoflavonoids demonstrated anti-acetylcholinesterase activity.⁵⁷ Generally, the biological effects of these compounds have not been thoroughly investigated. The chemical structures of pongapin and pongaglabrone are shown as Table 1.

Recently, computational methods have improved our understanding of herbal medicine interactions, aiding practitioners in rationally designing herbal formulations.⁵⁸ To further assess their potential as anti-diabetic agents, we conducted *in silico* and *in vitro* studies to evaluate the α -glucosidase inhibitory activities of these compounds. These investigations lay the groundwork for the discovery of naturally occurring α -glucosidase inhibitors and provide insights into the mechanisms by which *P. pinnata* extract may exert its anti-diabetic effects.

Materials and Methods

Two furanoflavonoids candidates, pongaglabrone and pongapin, were isolated from *Pongamia pinnata* and collected from our previous study.⁵⁶

Alpha-glucosidase inhibition assay

Yeast α -glucosidase, *p*-nitrophenyl- α -D-glucopyranoside (pNPG), and 4-nitrophenol were obtained from Sigma. The α -glucosidase enzyme inhibition assay was carried out according to the method described in our previous work.⁵⁹ In brief, 20 μ L of α -glucosidase solution (0.5 U/mL) and 130 μ L of 100 mM phosphate buffer (pH 6.8) were added to each well. Subsequently, 50 μ L of the test sample at varying concentrations was added. The mixture was incubated at 37 °C for 15 min. Following pre-incubation, 50 μ L of 5 mM pNPG was introduced to initiate the reaction. After incubating at 37 °C for 5 min, the absorbance was measured at 405 nm using a microplate reader (Biotek, USA). The inhibitory activity was calculated using the following equation: α -glucosidase inhibition (%) = $(1 - A/A_c) \times 100$, where A represents the absorbance of the sample and A_c represents the absorbance of the control. Absorbance values for blank samples (reaction solutions without enzyme) were subtracted prior to calculation.

Statistical Analysis

The data were presented as $M \pm SD$ from three independent experiments. The half-maximal inhibitory concentration (IC_{50}) was determined using TableCurve 2D software (v4.0, Systat Software Inc.). One-way analysis of variance (ANOVA) employed to compare the IC_{50} values between compounds. A P -value < 0.05 was considered to indicate statistical significance.

Density functional theory (DFT) calculation

Becke's three-parameter and Lee-Yang-Parr hybrid functional (B3LYP)^{60,61} DFT method was combined with the 6-311++G(d,p) basis set to optimize PPE1 and PPE8 molecules in the gas phase. The geometric parameters are given in Supplementary Table S1. Meanwhile, the DFT/B3LYP/cc-pVTZ level of theory was calculated for the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital). The spectrum of the density of states (DOS) was also obtained using the GaussSum program.⁶² All DFT calculations were performed using Gaussian 09 programs⁶³ and GaussView⁶⁴ to represent the results.

Protein and Ligand Preparation

The 3D structure of α -glucosidase (PDB ID: 5NN8) was obtained from the Protein Data Bank. Following the methodology outlined in our previous publication,⁶⁵ water molecules, co-ligands, and heteroatoms were removed using Discovery Studio 2020. Subsequently, Autodock Tools (version 1.5.6) was used to add polar hydrogens and Kollman charges to the protein.⁶⁶ The prepared protein was then exported into a dockable pdbqt format for molecular docking. The 3D structures of the ligands were retrieved from the PubChem database, hydrogen atoms were added to each ligand, and the files were converted to pdbqt format using Open Babel 3.1.1 for docking.⁶⁷

Molecular Docking

Molecular docking was performed using AutoDock Vina (version 1.2). The binding pocket was defined based on the binding site of the co-ligand, Acarbose, with grid dimensions set according to the parameters established in our previous study.⁵⁹ Molecular interactions between the proteins and ligands were visualized using the BIOVIA Discovery Studio Visualizer 2020.

Molecular Dynamic Simulation

Molecular dynamics simulations were performed using GROMACS version 2020.4, following the procedures outlined in our previous publication.⁶⁸ System preparation was carried out with the CHARMM-GUI interface, utilizing the CHARMM36 force field. Trajectory and energy data were collected every 10 ps. The system was explicitly solvated using the TIP3P water model, and potassium chloride ions were introduced to achieve neutrality. Production simulations were conducted at a steady temperature of 300 K and a pressure of 1 atm, with the complex dynamics being simulated for 200 ns.

Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) studies

The drug-likeness of the compounds was evaluated based on Lipinski's rule of five. ADME properties, including absorption, distribution, metabolism, and excretion, were analyzed using the SwissADME server.⁶⁹ Furthermore, acute oral toxicity was predicted using the DL-AOT prediction server.^{70,71} In this study, we evaluated the prediction and significant descriptors of potential inhibitory compounds as mutagenicity and toxicological dosage level for different tissues using the PreADMET server.^{72,73}

Results

Alpha Glucosidase Assay

The *in vitro* α -glucosidase inhibitory activities of pongapin and pongaglabrone were evaluated, and the results are summarized in **Table 1**. Pongapin demonstrated inhibitory activity with an IC_{50} value of 116.5 ± 5.02 μ g/mL, while pongaglabrone exhibited a similar level of inhibition, showing an IC_{50} value of 137.10 ± 14.67 μ g/mL ($P > 0.05$). Notably, both compounds displayed stronger inhibitory effects than acarbose, which showed an IC_{50} value of 160.99 ± 14.3 μ g/mL ($P < 0.05$).

Frontier Molecular Orbitals

Frontier molecular orbitals (FMOs) are called the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital). The HOMO and LUMO energy values for pongapin and pongaglabrone molecules are -5.912 and -1.881 eV, and -6.188 and -1.930 eV, respectively, as

Table 2. The energy of HOMO/LUMO orbitals and chemical reactivity descriptors values of investigated compounds were calculated at DFT/B3LYP/cc-pVTZ.

Parameters	Compounds	
	Pongapin	Pongaglabrone
HOMO energy, E_{HOMO} (eV)	−5.912	−6.188
LUMO energy, E_{LUMO} (eV)	−1.881	−1.930
The energy gaps, E_g (eV)	4.031	4.258
Ionization potential, I (eV)	5.912	6.188
Electron affinity, A (eV)	1.881	1.930
Electronegativity, χ (eV)	3.896	4.059
Chemical hardness, η (eV)	2.016	2.129
Chemical potential, μ (eV)	−3.896	−4.059
Chemical softness, S (eV)	0.248	0.235
Electrophilicity, ω (eV)	3.766	3.869

shown in **Table 2**. From these values, it is evident that the HOMO and LUMO orbitals are localized in the benzene ring. Pongapin and pongaglabrone had an energy gap (E_g) between HOMO-LUMO values of 4.031 eV and 4.258 eV, respectively. The graphical representation of the DOS plot and HOMO-LUMO energy is shown in **Figure 1**.

Through the application of Koopman's theorem⁷⁴ ionization potential (I) was calculated as $-E_{\text{HOMO}}$, and electron affinity (A) was calculated as $-E_{\text{LUMO}}$. Subsequently, global chemical reactivity indices, electronegativity (χ), chemical hardness (η), chemical potential (μ), chemical softness (S), and electrophilicity (ω) values can be represented by the equation provided below⁷⁵:

$$\chi = (I + A) / 2 \quad (1)$$

$$\eta = (I - A) / 2 \quad (2)$$

$$\mu = -\chi \quad (3)$$

$$S = 1 / 2\eta \quad (4)$$

$$\omega = \mu^2 / 2\eta \quad (5)$$

The detailed calculation results are presented in **Table 2**. Observing the results from data suggests that both pongapin and pongaglabrone exhibit a more favorable electrophilicity (ω) nature. For pongapin, the calculated ω is 3.766 eV. For the molecule pongaglabrone, the high electrophilicity (ω) was observed at 3.869 eV. The presented ω value indicates the pongaglabrone molecule's capacity to accept electrons from the environment; thus, it has a higher binding capacity with biomolecules and can act as an electrophilic species.^{76,77} The good electron-accepting ability is also indicated by the high electronegativity (χ) value of 4.059 eV.

Molecular Docking Analysis

Molecular docking revealed that pongaglabrone interacts with α -glucosidase through one hydrogen bond at Arg600 and three hydrophobic interactions with Phe525, Trp481, and Asp616 (**Figure 2A**). Similarly, pongapin interacts with α -glucosidase through four residues: Arg600, Phe525, Trp481, and Asp616. The docking scores were -7.929 kcal/mol for pongaglabrone and -7.564 kcal/mol for pongapin, compared to -7.156 kcal/mol for acarbose. The interaction details and binding conformations are illustrated in **Figures 2** and **3**.

Molecular Dynamic Simulation

Molecular dynamics simulations were conducted to validate the docking results (**Figure 4**). The complex between pongaglabrone and the protein remained stable throughout the simulation, with RMSD fluctuations of approximately 1 Å. This indicates stable binding of both ligands at the docking site. Pongaglabrone formed at least one hydrogen bond during the initial 100 ns of simulation. Although no hydrogen bonds were observed between pongaglabrone and the protein after 100 ns, both RMSF and RMSD analyses showed no significant conformational changes in the ligand. Similarly, the complex between pongapin and the protein exhibited stability. During the first 100 ns of simulation, RMSD analysis indicated fluctuations of less than 0.2 Å in the complex and protein, after which the complex maintained a steady state. As shown in **Figure 4**, pongapin formed one or no hydrogen bonds with the protein throughout the simulation. RMSF analysis of both complexes revealed fluctuations primarily in the loops of the protein at the interaction site, while other parts of the protein remained stable throughout the simulation.

ADMET Studies

The *in silico* projections for the ADME (absorption, distribution, metabolism, and excretion) properties of pongapin and pongaglabrone are summarized in **Tables 3** and **4**. The results indicate that both compounds meet key criteria, suggesting high oral bioavailability. Specifically, pongapin and pongaglabrone have logS values of -4.61 and -4.43 , respectively, indicating moderate water solubility. Their TPSA values of 61.81 Å^2 and 71.04 Å^2 suggest that both compounds are likely to be efficiently absorbed in the intestines. Both compounds also have fewer than 10 rotatable bonds, reflecting a favorable balance of rigidity and flexibility. **Table 4** highlights that both compounds are anticipated to exhibit high gastrointestinal absorption and the ability to cross the blood-brain barrier. Their logKp values, which measure skin permeability, are comparable at -5.81 cm/s and -5.75 cm/s , respectively. The metabolism of these compounds involves several cytochrome P450 enzymes, including CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, which are crucial for drug

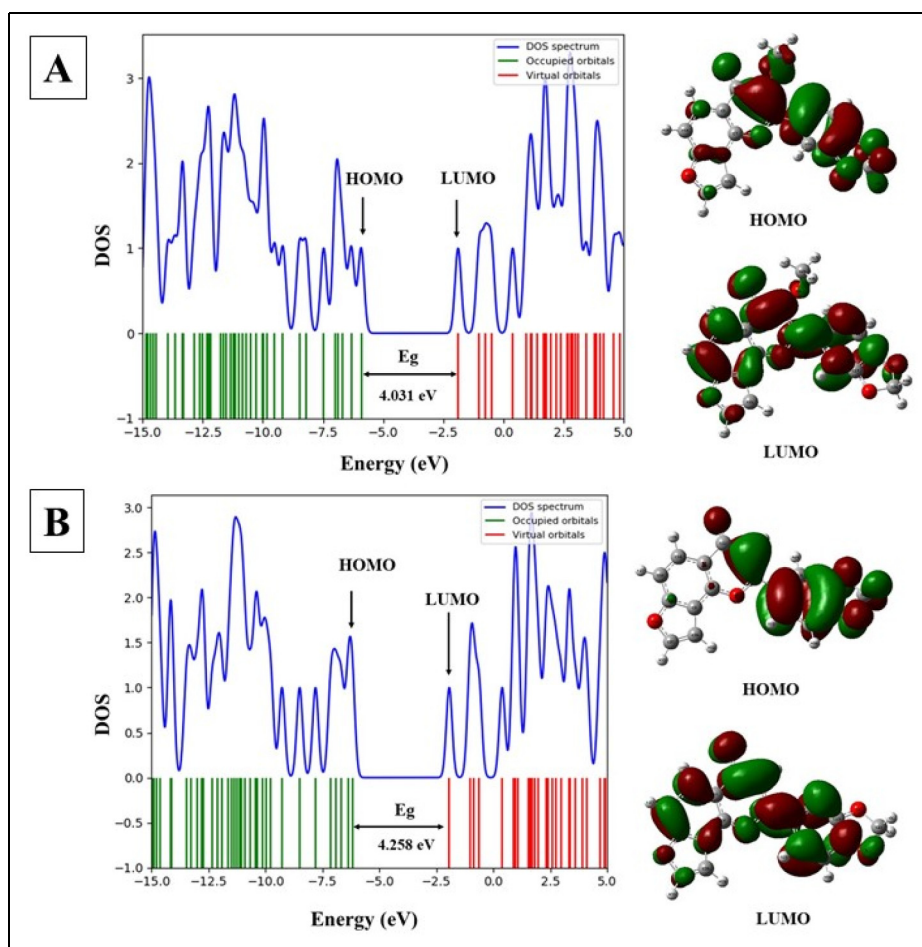


Figure 1. DOS plot and HOMO-LUMO energy gap of (A) pongapin and (B) pongaglabrone.

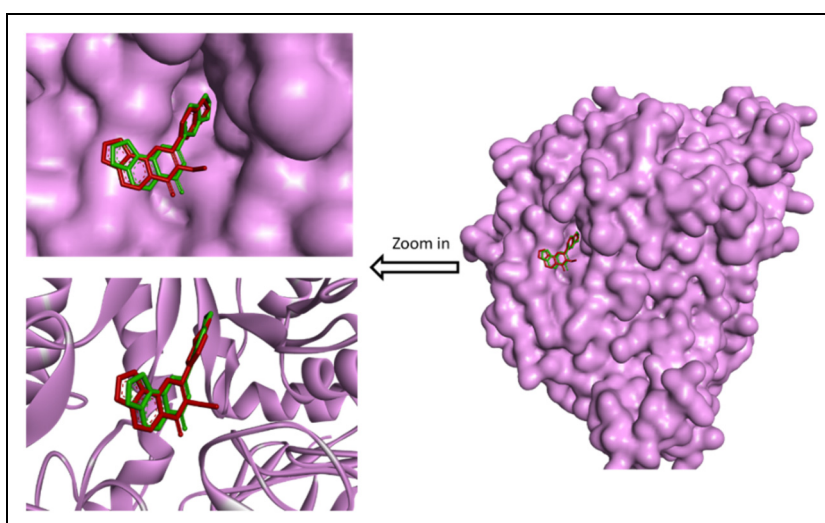


Figure 2. 3D interaction between compounds and α -glucosidase, pongaglabrone (green) and pongapin (red).

biotransformation. According to the SwissADME prediction program, neither compound is expected to be a substrate for P-glycoprotein (P-gp). Pongapin is predicted to inhibit

CYP1A2, CYP2C9, CYP2D6, and CYP3A4, while pongaglabrone is anticipated to inhibit CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4.

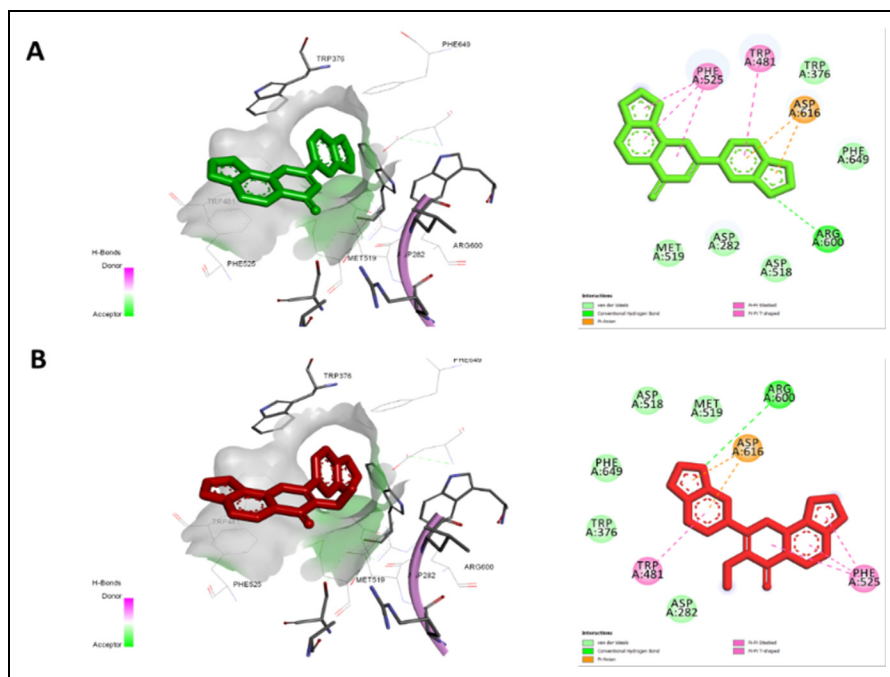


Figure 3. 3D and 2D interaction at docking site between compound and α -glucosidase (A) pongaglabrone (B) pongapin.

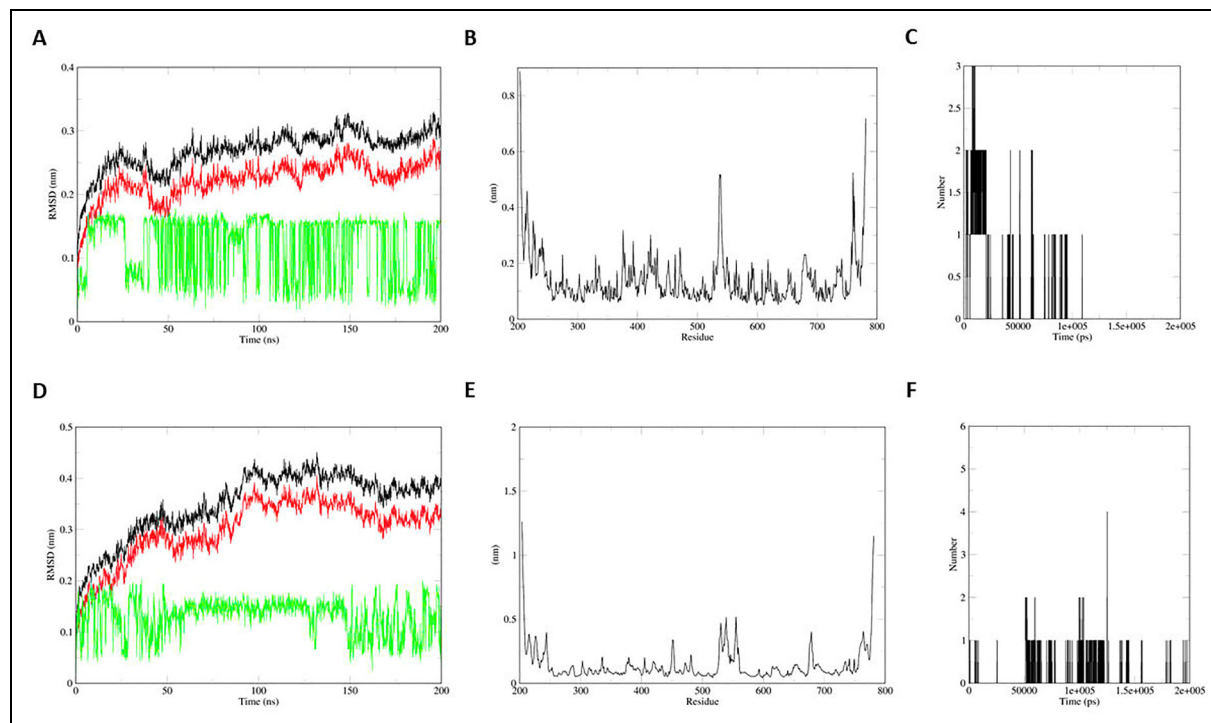


Figure 4. Molecular dynamic simulation of complex between compound and α -glucosidase over 200 ns. Pongaglabrone (above), pongapin (below). (A,D) RMSD. The black, red, and green colors represent the complex, protein backbone, and ligand, respectively (B,E) RMSF (C,F) number of hydrogen bond between ligand and protein.

Table 3. Drug Properties of Compounds with SwissADME.

Compound	Molecular weight (g/mol)	Log P	nHBD	nHBA	TPSA (Å ²)	MR	Lipinski Violation	Log Kp (cm/s)	Log S	nRotB
Pongapin	339.29	3.25	0	6	71.04	90.25	0	−5.81	−4.61	2
Pongaglabrone	306.27	3.23	0	5	61.81	83.75	0	−5.75	−4.43	1

MW, Molecular weight; LogP, Log of octanol/water partition coefficient; nHBD, Number of hydrogen bond donor(s); nHBA, Number of hydrogen bond acceptor(s); TPSA, Total polar surface area; MR, Molar refractivity; Log Kp, Log of skin permeation; Log S, log of solubility; nRotB, Number of rotatable bonds.

Table 4. ADME predictions of compounds computed by SwissADME.

Compound	Log Kp (cm/s)	GI Abs	BBB Per	Inhibitor Interaction					
				P-gp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor
Pongapin	−5.81	High	Yes	No	Yes	No	Yes	Yes	Yes
Pongaglabrone	−5.75	High	Yes	No	Yes	Yes	Yes	Yes	Yes

GI Abs: Gastro-intestinal absorption; BBB Per: Blood brain barrier permeability; P-gp, P-glycoprotein; CYP, cytochrome-P.

Table 5. Toxicity of Compounds Predicted by DL-AOT Prediction Server.

Compound	LD ₅₀ (mg/kg)	Label (probability)	Toxicity
Pongapin	2.95	3 (0.93)	caution
Pongaglabrone	3.30	3 (0.80)	caution

Toxicity Prediction

It is essential to assess the effects of pongapin and pongaglabrone on normal cells to ensure selectivity in disease treatment and to develop strategies that do not compromise patient safety. In this study, the DL-AOT prediction server was used to evaluate their potential toxicity. DL-AOT categorizes compounds into four risk groups: “danger/poison,” “warning,” “caution,” and “none required.” Based on LD₅₀ values of 2.95 and 3.30 mg/kg for pongapin and pongaglabrone, respectively, both compounds are classified as “caution,” indicating that caution is advised when considering their use in therapeutic applications. Although *in silico* data suggest that these compounds could effectively inhibit α -glucosidase, potentially aiding in diabetes treatment, their possible cytotoxicity necessitates further biological evaluation. Experimental studies are required to comprehensively understand their safety profiles and therapeutic potential (Table 5).

Based on preADME analysis, we determined that pongapin and pongaglabrone are likely to inhibit hERG, a potassium channel crucial for cardiac repolarization. Furthermore, these compounds showed mutagenic activity, testing positive with TA100_10RLI and TA100_NA but negative with TA1535_NA. However, mutagenic substances identified in the Ames test are not necessarily carcinogenic. Overall, the results in Table 6 suggest that pongapin and pongaglabrone possess low toxicity and carcinogenic risk. These findings, combined with further experimental validation, will aid in evaluating the compounds’ suitability for therapeutic development.

Discussion

The α -glucosidase inhibitory activities of pongapin and pongaglabrone, isolated from *Pongamia pinnata*, suggest the potential of this plant as a therapeutic aid for diabetes management. Both compounds exhibited IC₅₀ values lower than that of acarbose, indicating stronger inhibitory effects.

DFT calculation are significant for determining a molecule’s chemical reactivity and quantum chemical reactivity descriptors. The results indicate that the HOMO and LUMO orbitals are localized in the benzene ring. Notably, pongapin has a lower energy gap (Eg) than pongaglabrone, suggesting that the pongapin allows electrons to move more freely. This characteristic makes the molecule softer and may efficiently react with biomolecules with attendant biological activity.⁷⁸ FMO analysis further revealed that both pongapin and pongaglabrone possess high electrophilicity (ω) values, indicating their effectiveness as electron acceptors. These properties support their inhibitory potential against α -glucosidase, further validating their role as promising candidates for therapeutic applications.

Although pongaglabrone and pongapin demonstrated significant inhibitory activity against α -glucosidase in *in vitro* experiments, the underlying interactive mechanism remains unclear. In this study, we employed molecular modeling to elucidate the interactions between these ligands and the protein. We hypothesized that the compounds bind to the catalytic site, which is also the binding site of acarbose⁷⁹ with the furan ring fused to the flavonoid core enhancing interactions within the enzyme’s active site through hydrogen bonding, with the furan ring fused to the flavonoid core enhancing interactions within the enzyme’s active site through hydrogen bonding, π - π stacking, and hydrophobic interactions. The efficacy of both natural and synthetic furanoflavonoids in inhibiting α -glucosidase further underscores their potential as therapeutic agents for diabetes management.⁸⁰ These docking scores are quite similar to previous studies in the search for α -glucosidase inhibitory compounds.^{81,82}

Table 6. Mutagenicity and toxicological dosage level for different tissues of compounds by PreADMET server.

Test	Value	
	Pongapin	Pongaglabrone
Acute algae toxicity	0.0827983	0.072349
Ames test	mutagen	mutagen
Carcinogenicity (Mouse)	negative	negative
Carcinogenicity (Rat)	positive	positive
Acute daphnia toxicity	0.0931365	0.0645325
<i>In vitro</i> hERG inhibition	medium risk	medium risk
Acute fish toxicity (medaka)	0.0164603	0.00783716
Acute fish toxicity (minnow)	0.0138907	0.00564608
<i>In vitro</i> Ames test result in TA100 strain (Metabolic activation by rat liver homogenate)	positive	positive
<i>In vitro</i> Ames test result in TA100 strain (No metabolic activation)	positive	positive
<i>In vitro</i> Ames test result in TA1535 strain (Metabolic activation by rat liver homogenate)	negative	negative
<i>In vitro</i> Ames test result in TA1535 strain (No metabolic activation)	negative	negative

Molecular dynamics simulations further validated these findings by demonstrating stable binding interactions over 100 ns. The RMSD and RMSF fluctuations indicate the compounds' strong affinity and stable complex formation with α -glucosidase. The slight differences in binding efficiency between pongapin and pongaglabrone can be attributed to their structural variations, while their comparable docking scores confirm similar inhibitory potential.

For a drug to be considered suitable for oral administration, it generally must meet specific criteria, including a molecular weight between 150 and 500 g/mol, a topological polar surface area (TPSA) between 20 and 130 Å², a solubility (log S) no greater than -6, and no more than 9 rotatable bonds.⁶⁹ ADMET predictions confirmed that both pongapin and pongaglabrone meet the criteria demonstrating acceptable solubility, TPSA, and permeability properties. Despite meeting the parameters for oral bioavailability, the potential of these compounds to inhibit cytochrome (CYP) enzymes necessitates careful consideration of drug-drug interactions. Toxicity assessments further emphasize the need for experimental validation. While both compounds displayed low toxicity risks, their moderate hERG inhibition and mutagenic activity in specific assays warrant additional safety evaluations. hERG inhibition is particularly concerning as it can prolong the QT interval—a critical electrocardiogram parameter reflecting the duration of ventricular contraction—and may lead to potentially fatal ventricular arrhythmias.⁸³ Thus, caution is needed when using pongapin and pongaglabrone, particularly in cardiovascular patients.^{84,85}

Overall, pongapin and pongaglabrone demonstrate promising inhibitory activity against α -glucosidase, suggesting potential for therapeutic applications. However, further optimization is

necessary to fully realize their clinical utility. Future research should focus on experimental validation, structural refinement, and comprehensive toxicological profiling to ensure their safety and efficacy. Additionally, confirming the precise binding interactions of pongapin and pongaglabrone with α -glucosidase through experimental methods is critical. Cell-based and animal studies are also required to validate their bioactivity and thoroughly assess potential toxicity. Besides, a significant challenge is the limited natural availability of these compounds, underscoring the need for synthetic production and structural modifications to enhance their specific inhibitory activity and pharmacological properties.

Conclusion

The study demonstrates that pongapin and pongaglabrone exhibit significant α -glucosidase inhibitory activity, with IC₅₀ values of 116.5 ± 5.02 µg/mL and 137.10 ± 14.67 µg/mL, respectively. Molecular docking studies revealed binding affinities of -7.564 kcal/mol for pongapin and -7.929 kcal/mol for pongaglabrone. Molecular dynamics simulations further confirmed their inhibitory effects, supporting their potential as promising candidates for anti- α -glucosidase therapy. However, ADMET predictions suggest that, although both compounds are absorbable via the digestive tract, they may pose toxicity risks.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Ethical Approval is not applicable for this article.

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Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Supplemental Material

Supplemental material for this article is available online.

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