



In-depth insights into the antidiabetic activity of *Dracaena trifasciata* (Prain) Mabb. fractions and subfractions: *In vitro* and computational studies

[Análisis en profundidad de la actividad antidiabética de fracciones y subfracciones de *Dracaena trifasciata* (Prain) Mabb.: Estudios *in vitro* y computacionales]

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Abstract

Context: *Dracaena trifasciata* Prain has shown potential in pharmaceutical research, particularly for its antidiabetic properties. Investigating its effects on α -glucosidase enzyme inhibition can provide insights into its role as an antidiabetic agent.

Aims: To evaluate the antidiabetic activity of the ethyl acetate fraction and subfractions from *D. trifasciata* against α -glucosidase through *in vitro* assay and analyze molecular interactions, absorption, distribution, metabolism, and excretion (ADME), toxicity, and stability through *in silico* studies.

Methods: An α -glucosidase enzyme assay was performed using the ethyl acetate fraction (FE), subfraction C (SC), and subfraction E (SE) at concentrations of 100, 200, 300, 400, and 500 $\mu\text{g/mL}$. Acarbose was used as the control. Computational docking, drug-likeness, ADME and toxicity analysis, molecular dynamics, and Molecular Mechanics, General Born Surface Area (MM/GBSA) energy analysis were conducted on methyl pyrophaeophorbide A and (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone from SE against α -glucosidase.

Results: At 500 $\mu\text{g/mL}$, the inhibition percentages for the FE, SC, SE, and acarbose (1 $\mu\text{g/mL}$) were 70.11%, 69.89%, 75.17%, and 72.20%, respectively. IC_{50} values were 170.82 $\mu\text{g/mL}$ (FE), 183.47 $\mu\text{g/mL}$ (SC), 74.89 $\mu\text{g/mL}$ (SE), and 0.29 $\mu\text{g/mL}$ (acarbose). Molecular docking showed (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone interacting with α -glucosidase via hydrogen bonds with Arg552 and hydrophobic interactions with Asp232, Trp329, Asp469, Asp568, and Phe601. Although the analysis results indicate a safer ADME profile and lower toxicity for methyl pyrophaeophorbide A compared to (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone. The (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone also demonstrated good stability and favorable binding energy (-33.86 kJ/mol) compared to acarbose.

Conclusions: Subfraction E of *D. trifasciata* demonstrates promising antidiabetic activity through α -glucosidase inhibition, with (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone showing strong binding affinity. These findings support further investigation of *D. trifasciata* as a potential source of novel antidiabetic agents.

Keywords: α -glucosidase; antidiabetic agents; blood glucose; molecular dynamic; natural product.

Resumen

Contexto: *Dracaena trifasciata* Prain ha demostrado su potencial en la investigación farmacéutica, en particular por sus propiedades antidiabéticas. La investigación de sus efectos sobre la inhibición de la enzima α -glucosidasa puede aportar información sobre su papel como agente antidiabético.

Objetivos: Evaluar la actividad antidiabética de la fracción de acetato de etilo y subfracciones de *D. trifasciata* contra la α -glucosidasa mediante ensayo *in vitro* y analizar las interacciones moleculares, absorción, distribución, metabolismo y excreción (ADME), toxicidad y estabilidad mediante estudios *in silico*.

Métodos: Se realizó un ensayo enzimático de α -glucosidasa utilizando la fracción de acetato de etilo (FE), la subfracción C (SC) y la subfracción E (SE) a concentraciones de 100, 200, 300, 400 y 500 $\mu\text{g/mL}$. Se utilizó acarbosa como control. Se llevaron a cabo análisis computacionales de acoplamiento, similitud a fármacos, ADME y toxicidad, dinámica molecular y Mecánica Molecular, Área de Superficie General Born (MM/GBSA) sobre metil pirofoporfida A y (2S)-3',4'-metilendioxi-5,7-dimetoxiflavona de SE contra α -glucosidasa.

Resultados: A 500 $\mu\text{g/mL}$, los porcentajes de inhibición para la FE, SC, SE y acarbosa (1 $\mu\text{g/mL}$) fueron 70.11%, 69.89%, 75.17% y 72.20%, respectivamente. Los valores de IC_{50} fueron 170,82 $\mu\text{g/mL}$ (FE), 183,47 $\mu\text{g/mL}$ (SC), 74,89 $\mu\text{g/mL}$ (SE) y 0,29 $\mu\text{g/mL}$ (acarbosa). El acoplamiento molecular mostró que la (2S)-3',4'-metilendioxi-5,7-dimetoxiflavona interactuaba con la α -glucosidasa mediante enlaces de hidrógeno con Arg552 e interacciones hidrofóbicas con Asp232, Trp329, Asp469, Asp568 y Phe601. Aunque los resultados del análisis indican un perfil ADME más seguro y una menor toxicidad para el metil pirofoporfida A en comparación con la (2S)-3',4'-metilendioxi-5,7-dimetoxiflavona. La (2S)-3',4'-metilendioxi-5,7-dimetoxiflavona también demostró una buena estabilidad y una energía de unión favorable (-33,86 kJ/mol) en comparación con la acarbosa.

Conclusiones: La subfracción E de *D. trifasciata* demuestra una prometedora actividad antidiabética a través de la inhibición de la α -glucosidasa, con (2S)-3',4'-metilendioxi-5,7-dimetoxiflavona mostrando una fuerte afinidad de unión. Estos resultados apoyan la investigación de *D. trifasciata* como fuente potencial de nuevos agentes antidiabéticos.

Palabras Clave: α -glucosidasa; agentes antidiabéticos; glucosa en sangre; dinámica molecular; producto natural.

ARTICLE INFO

Received: August 26, 2024.

Accepted: January 29, 2025.

Available Online: February 20, 2025.

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Abbreviations: ΔE_{TOTAL} : Total Binding Energy; ΔE_{ELE} : Electrostatic Energy; ΔE_{GB} : Generalized Born Energy; ΔE_{VDW} : van der Waals Energy; ΔE_{SURF} : Nonpolar Solvation Free Energy; ADME: Absorption, Distribution, Metabolism, and Excretion; CYP: Cytochrome P450; DPP-IV: Dipeptidyl peptidase-4; ESOL: Estimated SOLubility Model; FE: Ethyl acetate fraction; GI: Gastrointestinal; Log S: Solubility; MM/GBSA: Molecular Mechanics, General Born Surface Area; P-gp: P-glycoprotein; PPAR γ : Peroxisome proliferator-activated receptor gamma; PTP: Protein tyrosine phosphatase; RMSD: Root Mean Square Deviation; RMSF: Root Mean Square Fluctuation; SASA: Solvent-Accessible Surface Area; SC: Subfraction C; SE: Subfraction E; SGLT-1: Sodium-glucose co-transporter-1.

INTRODUCTION

As one of the World's mega-biodiverse countries with many plant species, Indonesia has great potential to develop into the center of natural-based medicine (Maskun et al., 2021). The biodiversity includes thousands of plant species, many of which have empirically proven medicinal properties. However, empirical data alone is insufficient with advances in technology and science. Scientific validation of the pharmacological effects of traditional medicine is necessary. One such plant that needs to be developed is *Sansevieria trifasciata* Prain (family *Asparagaceae*), a synonym of *Dracaena trifasciata* (Prain) Mabb. This plant is recognized for its medicinal properties, treating conditions like colds and diarrhea and promoting hair growth (Dewatisari et al., 2023). In Perak, Malaysia, indigenous people use it to treat earaches, fever, wounds (Afrasiabian et al., 2016), bronchitis, asthma, toxemia, and insect bites (Andhare et al., 2012). In addition to treating several symptoms and diseases, interestingly, this plant can also be used to treat metabolism-related diseases such as diabetes mellitus. In South Sumatra, Indonesia, people traditionally used the exudate and roots from this plant for diabetic treatment (Hartanti and Budipramana, 2020). Based on this empirical information, many researchers consider it important to further study this plant due to its potential pharmacological effects. A study conducted explorations related to the chemical compounds found in this plant. Several compounds suspected to play a role in pharmacological activity include kaempferol and quercetin, which have been identified as major compounds (Babu and Prabhu, 2024). In another study, these chemical compounds were found to be active as antihyperglycemic agents through mechanisms involving the inhibition of enzymes such as amylase, dipeptidyl peptidase-4 (DPP-IV), peroxisome proliferator-activated receptor gamma (PPAR γ), protein tyrosine phosphatase (PTP), and sodium-glucose co-transporter-1 (SGLT-1) (Ali et al., 2024). Pregnane glycoside derivatives have also been reported to be present in *S. trifasciata* (Mimaki et al., 1997). In a separate study, pregnane glycoside derivatives were found to inhibit amylase activity *in vitro*, making them potential compounds for lowering blood glucose levels (Ogunyemi et al., 2022).

Research advancements in using medicinal plants for treating diabetes mellitus indicate that *D. trifasciata* is a promising plant that warrants further explo-

ration and development. An *in vivo* assay on streptozotocin-induced diabetic rats showed that this plant extract may reduce reactive oxygen species levels, repair and protect injured tissue, and reduce hyperglycemia-induced cell death (Dey et al., 2014). In a different study, *S. trifasciata* extracts (distilled water, ethanol, and ethyl acetate) inhibited α -glucosidase, with ethyl acetate having the lowest IC₅₀ value. The ethyl acetate fraction holds the potential for further advancement as a prospective therapeutic (Yumna et al., 2018). *In vivo* assay was also conducted by administering *S. trifasciata* decoction to the animal model. The results showed a decrease in blood glucose levels and an increase in granule density in the β cells of the islets of Langerhans in alloxan-induced hyperglycemic rats (Qomariyah et al., 2012). A similar study was also conducted using ethanol extract (Dey et al., 2014; Laimeheriwa et al., 2014). These research findings indicate that *S. trifasciata* exhibits promising potential as an antidiabetic agent. Nevertheless, the research findings were limited due to the use of specific samples. No investigation has been undertaken thus far regarding the antidiabetic properties of the fractions and subfractions of *S. trifasciata*. In fact, dividing the components in the extract into fractions and subfractions may effectively improve the concentration of active chemicals, thereby improving their pharmacological effectiveness (Conrado et al., 2024). *Dracaena trifasciata*, traditionally used to treat various ailments, has been extensively investigated for its phytochemical and pharmacological properties (Babu and Prabhu, 2024). The plant is known to contain flavonoids, stilbenoids, and other bioactive compounds exhibiting analgesic, anti-inflammatory, antimicrobial, and antioxidant activities (Thu et al., 2020). Furthermore, *in silico* studies have identified potential phytochemicals from *D. trifasciata* capable of inhibiting key enzymes implicated in rheumatoid arthritis, highlighting its therapeutic potential (Ahmed et al., 2022). While the antidiabetic properties of *D. trifasciata* have not been extensively studied, the plant has traditionally been used for a variety of medicinal purposes (Babu and Prabhu, 2024). Therefore, this study explores the antidiabetic activity of the fractions and subfractions of *D. trifasciata* through *in vitro* and *in silico* approaches.

Diabetes mellitus is a medical condition defined by impaired insulin production by pancreatic β -cells and the failure of insulin-sensitive tissues to properly re-

act to insulin (Galicia-Garcia et al., 2020). This condition is treated by taking antidiabetic medicines that act via many molecular pathways, including inhibiting the enzyme α -glucosidase (Meneses et al., 2015). This enzyme is crucial in the further fragmentation of carbohydrates into glucose units by cleaving glucosidic bonds (Khirallah et al., 2022). The high number of glucose units produced will lead to an increase in postprandial blood glucose levels, which is unlikely to occur in patients with pancreatic injury or insulin resistance conditions. This must be managed for a relatively extended period of time using α -glucosidase inhibitors. Therefore, the pursuit and advancement of novel pharmaceuticals that target this enzyme persist. Subsequently, this study focuses on the antidiabetic determination of ethyl acetate fraction, subfraction C and E against α -glucosidase enzyme, and continues with molecular interaction predictions between the compound from subfractions against α -glucosidase enzyme.

MATERIAL AND METHODS

Extraction and fractionation processes

Leaves of *D. trifasciata* were collected from Unaaha District, Konawe Regency, Southeast Sulawesi Province (3°50'15.8" S 122°02'55.0" E). The *D. trifasciata* leaves were identified by the School of Life Sciences and Technology, Bandung Institute of Technology, West Java, Indonesia, under registration number 6470/11.CO2.2/PL/2019. The leaves were processed by washing, cutting, drying at 50°C, and grinding into powder. The powder (3500 grams) was macerated with ethanol, yielding 467.46 grams of crude extract. This extract was fractionated using ethyl acetate and further purified via column chromatography with silica gel 60H₂₅₄ p.a (E. Merck). The chromatography, conducted with gradient elution of n-hexane: EtOAc: MeOH, produced sixteen subfractions. These subfractions were combined based on TLC profiles, resulting in two major subfractions: C (subfractions 8-9, with a 25% w/w yield) and E (subfractions 11-14, with a 12% w/w yield), which were used for further analysis.

Preparation of solutions

Sodium carbonate solution (Na₂CO₃) 200 mM preparation

Na₂CO₃ (5.3 g) was dissolved in 250 mL of CO₂-free water to obtain a solution with a concentration of 200 mM (Maryam et al., 2020).

Acarbose preparation

A solution with a concentration of 10 ppm was prepared by dissolving 1 mg of acarbose in 100 mL of phosphate buffer at pH 7. Subsequently, this solution

was diluted to create a series of concentrations ranging from 0.2 to 1 ppm (Maryam et al., 2020).

Dracaena trifasciata samples preparation

The samples that were used in this study were ethyl acetate fraction, subfraction C, and subfraction E from *S. trifasciata* (a synonym of *Dracaena trifasciata*) obtained in our previous study (Kasmawati et al., 2022). These subfractions are reported to contain alkaloid derivatives (methyl pyropheophorbide A) and flavonoid derivatives [(2S)-3',4'-methylenedioxy-5,7-dimethoxyflavane], which are potentially responsible for their antidiabetic activity. Each sample (10 mg) was mixed with phosphate buffer pH 7 (10 mL). This made a stock solution with a 1000 ppm concentration, and then five different concentrations of samples 100, 200, 300, 400, and 500 ppm were made (Maryam et al., 2020).

p-Nitrophenyl- α -D-glucopyranoside (PNPG) substrate solution

To prepare the substrate solution, 15.062 mg of PNPG were dissolved in 10 mL of deionized water to achieve a final concentration of 5 mM (Maryam et al., 2020).

α -Glucosidase enzyme solution

The stock solution was prepared by weighing the α -glucosidase enzyme (1 mg) and dissolving it in phosphate buffer pH 7 (100 mL) (in each mg there was 28 U). A volume of 0.089 mL of the stock solution was diluted with phosphate buffer at pH 7 to a final volume of 10 mL, resulting in an enzyme solution with a concentration of 0.25 U/mL (Maryam et al., 2020).

Inhibition of α -glucosidase enzyme assay

The antidiabetic activity of compounds against α -amylase was evaluated using a standardized procedure across three solution types: blank, acarbose comparative control, and test solutions derived from fractions and subfractions of *D. trifasciata*. Initially, 36 μ L of phosphate buffer (pH 7) was combined with 17 μ L of 5 mM PNPG and incubated in a water bath at 37°C for 5 minutes. Subsequently, 17 μ L of α -glucosidase enzyme was added to the mixture, followed by an additional incubation for 15 minutes at 37°C. The reaction was halted by adding 100 μ L of 200 mM Na₂CO₃, and absorbance was measured at 405 nm using an ELISA reader (Maryam et al., 2020).

For the blank solution, only the phosphate buffer and PNPG mixture were utilized. The acarbose comparative control involved the addition of 30 μ L of acarbose solution at concentrations of 0.2, 0.4, 0.6, 0.8,

and 1 ppm. Test solutions from *D. trifasciata* consisted of 30 µL of ethyl acetate fractions and subfractions C and E at concentrations of 100, 200, 300, 400, and 500 ppm.

Molecular docking study

The crystallographic structure of the α -glucosidase enzyme was used to study the molecular interactions of compounds from subfraction E of *D. trifasciata* with the identity code ID 3W37 (Tagami et al., 2013). This enzyme structure is known to crystallize with acarbose, which is the native ligand. Water molecules and bound ligands were separated from the enzyme, and with the help of AutoDock Tools v1.5.6, the enzyme was protonated, and Kollman charges were added (Morris et al., 2009). Meanwhile, the most effective compound from subfraction E of *D. trifasciata*, identified in our previous study (Kasmawati et al., 2022), was prepared using AutoDock Tools v1.5.6 following the procedures outlined in that study. The binding affinity and interactions of the compounds were evaluated using AutoDock Vina. The docking procedure details followed the steps described in our previous study (Arfan et al., 2024). The α -glucosidase binding site was defined with coordinates $x = 0.301$, $y = -1.798$, and $z = -23.212$ with a cubic search grid size of 20 Å on each side.

Molecular dynamics simulation

In this research, classical molecular dynamics simulations of the α -glucosidase enzyme in complex with compounds from subfraction E of *D. trifasciata* were conducted using GROMACS version 2024.2 (Abraham et al., 2015), employing the AMBER99SB-ILDN force field (Petrov and Zagrovic, 2014). The topologies for the compounds were generated using Antechamber in AmberTool 2024, executed within the ACPYPE environment (Silva and Vranken, 2012), which integrates the General Amber force field (Wang et al., 2004). The initial structures for the molecular dynamic simulations were derived from the complexes identified in our molecular docking studies. The TIP3P water model was used to hydrate these systems, which were positioned inside a simulation box (Arfan et al., 2022). Ions were introduced to achieve system neutralization. Energy minimization was initiated using the steepest descent method, with a maximum of 50,000 steps, terminating when the forces fell below 1000 kJ/mol/nm. Subsequently, an NVT equilibration phase was performed for 1 ns at a constant temperature of 310 K, utilizing the V-rescale algorithm. This was followed by a 2 ns NPT equilibration phase, during which the Berendsen barostat maintained the pressure at 1 bar. To address long-range electrostatic interactions within the system, the parti-

cle mesh Ewald method was employed (Wang et al., 2016). Finally, the complex systems underwent a 100 ns production run, using a timestep of 2 fs and saving trajectories every 10 ps. The stability of all complex systems was analyzed, and their binding energies were calculated using the MM/GBSA approach with the assistance of gmx_mmpbsa (Valdés-Tresanco et al., 2021).

ADME, toxicity and drug likeness analysis

A computational methodology was applied to assess the pharmacokinetic characteristics of the compounds identified in the *D. trifasciata* subfraction, focusing on parameters such as absorption, solubility, P-glycoprotein (P-gp) membrane transport, and metabolism, using the SwissADME webserver (<http://www.swissadme.ch/index.php>) (Daina et al., 2017). Additionally, the evaluation of drug-likeness properties was conducted in accordance with Lipinski's rule of five, employing the same platform (Benet et al., 2016). The toxicity potential of the compounds was further predicted through the ProTox 3.0 webserver (<https://tox.charite.de/protox3/index.php?site=home>), encompassing key toxicity parameters such as hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity.

Statistical analysis

The percentage of inhibition was determined by utilizing the absorbance data from samples and controls by the formula [1] (Ouassou et al., 2018).

$$\text{Inhibitory activity (\%)} = \frac{B-S}{B} \times 100 \quad [1]$$

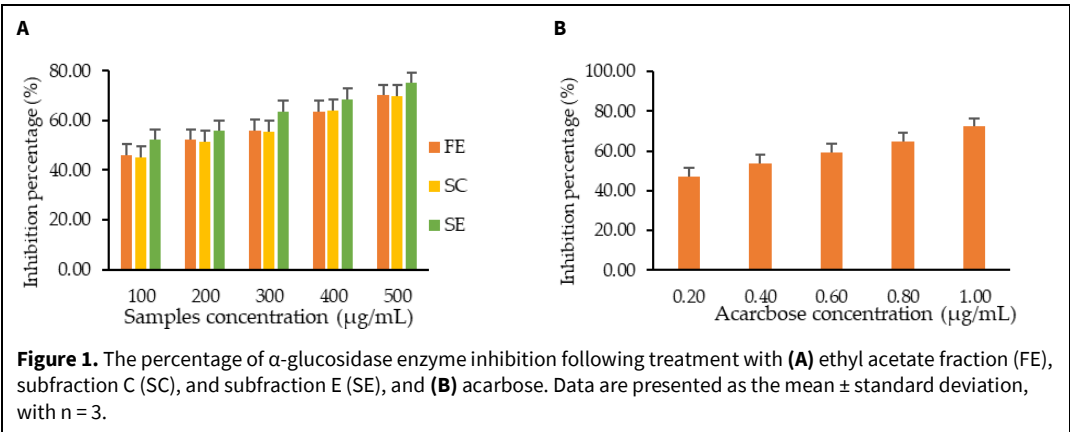
Where B represents the absorbance of the blank, while S denotes the absorbance of the fraction and the subfractions (the difference between the absorbance measured with the enzyme and without the enzyme). Furthermore, the linear regression equation was used to determine the IC₅₀ value based on the equation below, where 'a' represents the intercept and 'b' represents the slope.

$$\text{IC}_{50} = \frac{(50-a)}{b} \quad [2]$$

Subsequently, the inhibition data and the IC₅₀ values were presented as mean $\pm$ SD, with triple data replication for each sample ($n = 3$). The IC₅₀ values for each sample were statistically analyzed using the one-way ANOVA method, followed by LSD post-hoc testing, by using the IBM SPSS Statistics® version 24, with a significance level ($p > 0.01$, 1%).

In silico data analysis

In silico data analysis for drug discovery, several steps were used using specific computational tools. Molecular docking began with the preparation of



ligand and receptor structures and the validation of docking methods by applying RMSD criteria. The binding energy resulting from the docking results was compared with acarbose as a reference. Prediction of ADME and drug-likeness of compounds was carried out using the SwissADME webserver, and toxicity was assessed using ProTox 3.0 webserver. Molecular interactions such as hydrogen bonds and hydrophobic contacts of compounds from *D. trifasciata* against α -glucosidase enzyme were visualized using Discovery Studio Visualizer software. The stability of all complex systems derived from molecular dynamics simulations was assessed through the analysis of Root Mean Square Deviation (RMSD), Root Mean Square Fluctuation (RMSF), and Solvent Accessible Surface Area (SASA). Additionally, binding energies were calculated using the Molecular Mechanics/Generalized Born Surface Area (MM/GBSA) approach, facilitated by the gmx_MMPBSA tool.

RESULTS

Antidiabetic activity of *D. trifasciata*

Samples of *D. trifasciata* have the potential to inhibit the α -glucosidase enzyme in a concentration-dependent manner. Each sample's absorbance measurements from the ELISA reader were converted to a percentage inhibition (Fig. 1A). The findings indicated that the percentage of inhibition increased along with the sample's concentration. The sample with the highest percentage of inhibition at a concentration of 500 $\mu\text{g/mL}$ was subfraction E (SE), followed by the ethyl acetate fraction (FE) and subfraction C (SC), with values of 75.17%, 70.11%, and 69.89%, respectively. The positive control exhibited the highest percentage of inhibition at a concentration of 1 $\mu\text{g/mL}$, which was 72.20% (Fig. 1B). This result indicated that the SE and FE exhibit comparable inhibition data to the positive control. The percentage inhibition data was subsequently transformed into IC_{50} values. The results indicated that the acarbose control exhibited potent inhi-

bition, with an $\text{IC}_{50} < 50 \mu\text{g/mL}$ (Table 1). The samples exhibited different levels of inhibitory potency, with SE showing a strong inhibitory effect (IC_{50} 50-100 $\mu\text{g/mL}$) (Widiastuti et al., 2024), while FE and SC exhibited a weak inhibitory effect ($\text{IC}_{50} > 151 \mu\text{g/mL}$). The FE, SC, and SE samples had the potential to inhibit the α -glucosidase enzyme, but the therapeutic effectiveness was significantly different from acarbose ($p < 0.01$) (Table 1), which indicated that acarbose was still more effective in inhibiting α -glucosidase than the samples.

Table 1. IC_{50} values of the samples against the α -glucosidase enzyme.

Samples	$\text{IC}_{50} \pm \text{SD} (\mu\text{g/mL})$
Acarbose	0.29 ± 0.01
FE	170.82 ± 0.15^a
SC	183.47 ± 0.18^a
SE	74.89 ± 0.49^a

^aMean significantly different ($p < 0.01$) to the positive control acarbose.

Molecular interaction analysis

The binding modes of a ligand to an enzyme were predicted using molecular docking analyses, focusing on binding affinity and interactions with amino acid residues. This analysis concentrated on the interactions between compounds from *D. trifasciata*, particularly those in subfraction E (SE), such as methyl pyropheophorbide A and (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone, with the enzyme α -glucosidase, which is crucial for glucose regulation. To verify the docking procedure, acarbose was redocked, and its RMSD was measured. A lower RMSD value indicates the docking parameters more accurately reproduce the ligand's reference conformation observed in X-ray crystallography and was used as a validation measure (Aman et al., 2023). These compounds showed inhibitory effects on their target enzymes, offering essential insights into the active sites, which serve as reference

points for simulating interactions between the compounds and the target enzyme (Arfan et al., 2024).

The α -glucosidase complex with acarbose was selected as the enzyme model due to the well-established inhibitory characteristics of the ligand. Redocking analysis demonstrated that the best conformation of acarbose within the α -glucosidase binding site closely matched the pose reported in X-ray crystallography (RMSD 0.893 Å) (Fig. 2). In this docking study, methyl pyrophosphoride A and (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone showed stronger affinities for α -glucosidase compared to acarbose (-7.5 kcal/mol), with binding energies of -8.2 kcal/mol and -7.8 kcal/mol, respectively.

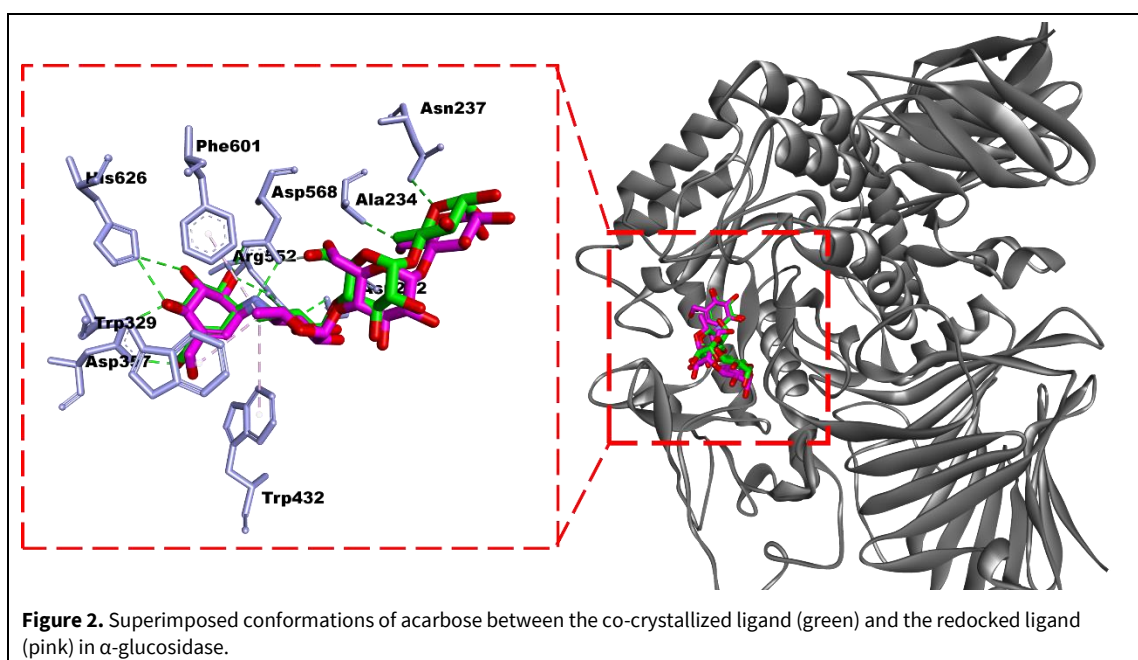
Acarbose was observed to form seven substantial hydrogen bonds with α -glucosidase, predominantly contributed by its hydroxyl groups (Fig. 2). These extensive hydrogen bonds significantly contribute to the stability and affinity of acarbose within the enzyme's active site. Additionally, acarbose established hydrophobic interactions with residues Trp329, Trp432, and Phe601, which further stabilize the ligand-enzyme complex through non-polar interactions.

Interestingly, methyl pyrophosphoride A formed three hydrogen bonds with Ser505, Lys506, and Asn237. These interactions suggest a strong and specific binding affinity to these residues, potentially enhancing the inhibitory effect on α -glucosidase. Furthermore, methyl pyrophosphoride A exhibited hydrophobic interactions with residues Ile233, Phe236, Phe476, and Ala602 (Fig. 3A), indicating a

robust non-polar interaction network that contributes to the compound's binding stability. Meanwhile, (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone formed hydrogen bonds with Arg552, a critical interaction that anchors the compound within the active site of α -glucosidase. This compound also demonstrated hydrophobic interactions with Asp232, Trp329, Asp469, Asp568, and Phe601 (Fig. 3B). The presence of these hydrophobic interactions suggests that (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone effectively occupies the enzyme's active site, thereby potentially inhibiting its activity.

Molecular stability analysis

The stability of the two compounds from *D. trifasciata* was verified through a 100 ns molecular dynamics (MD) simulation. The analysis focused on assessing the stability of the α -glucosidase and compound complexes. During the simulation, it was observed that the C-alpha (C α) of the enzyme complexed with acarbose exhibited the highest RMSD of 2.46 Å (Table 2). Notably, when the enzyme interacted with the compounds from *D. trifasciata*, it demonstrated even greater stability than with acarbose. Specifically, the RMSD values were 2.22 Å for (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone and 2.42 Å for methyl pyrophosphoride A (Fig. 4). Furthermore, the stability of the *D. trifasciata* compounds was found to be lower compared to acarbose, with RMSD ligand values of 0.49 Å and 1.50 Å for (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone and methyl pyrophosphoride A, respectively (Fig. 5).



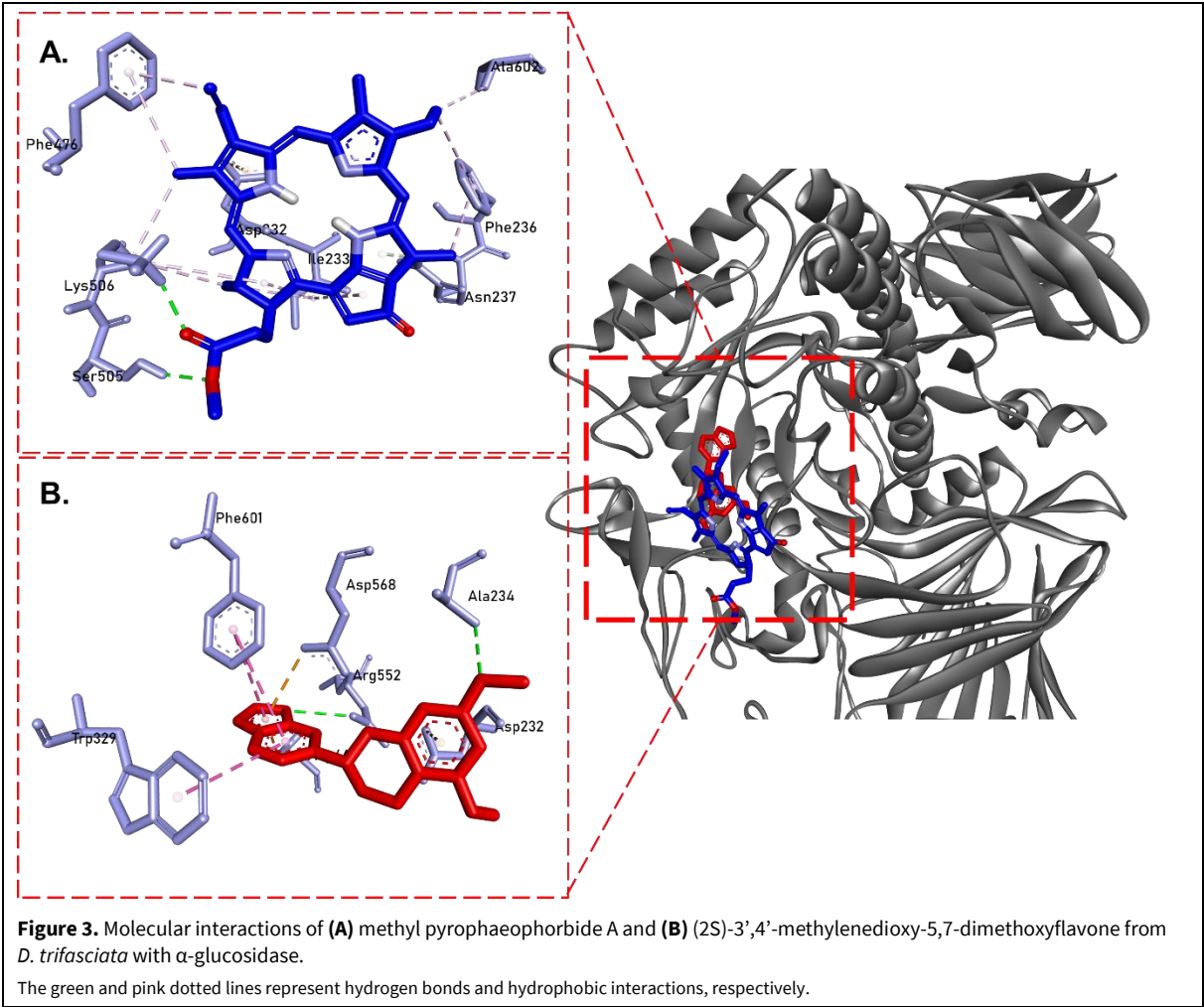


Table 2. The mean RMSD of the enzyme's C α and the mean RMSD of the ligands in the α -glucosidase system.

Complex system	Mean RMSD enzyme C α atom (Å)	Mean RMSD of ligand (Å)
Acarbose	2.46 $\pm$ 0.18	2.60 $\pm$ 0.54
(2S)-3',4'-Methylenedioxy-5,7-dimethoxyflavone	2.22 $\pm$ 0.14	0.49 $\pm$ 0.08
Methyl pyrophaeophorbide A	2.42 $\pm$ 0.15	1.50 $\pm$ 0.23

Throughout the simulation, RMSF values for each complex were monitored, as depicted in Fig. 6. The RMSF graph offers comprehensive insights into the fluctuations of amino acid residues in α -glucosidase over the 100 ns simulation period. All complexes exhibited a consistent pattern of residue fluctuations, with some residues showing marked oscillations. Notably, residues Glu39, Ser55, Arg856, Gly885, and Glu909 exhibited significant fluctuations.

Importantly, the RMSF graph revealed that the *D. trifasciata* compounds stabilized α -glucosidase amino acid residues, resulting in reduced fluctuations compared to acarbose, particularly at residues Ser55, Phe364, Ser406, Arg447, Ile821, Arg840, and Gly885. This observation suggests that (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone, and methyl

pyrophaeophorbide A may establish more stable interactions with α -glucosidase, potentially enhancing their inhibitory activity against this enzyme.

To comprehensively assess the stability of each compound from *D. trifasciata*, we calculated the solvent-accessible surface area (SASA) for each complex system. This method provides important insights into the folding and stability of the complex by tracking changes in the protein's solvent area throughout the simulation (Fig. 7). A lower SASA value indicates a more stable ligand-enzyme complex. The SASA analysis revealed that all compounds displayed a similar range of solvent-accessible areas. The average SASA values for the complexes were 308.08 nm² for acarbose, 307.65 nm² for (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone, and 306.27 nm² for methyl py-

ropheophorbide A. Notably, (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone demonstrated exceptional stability, as indicated by its relatively unchanged SASA value throughout the experiment. This suggests that (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone forms strong interactions with α -glucosidase, thereby enhancing its stability within the complex.

MM-GBSA analysis

The binding efficiency of phytoconstituents from *D. trifasciata* to α -glucosidase was assessed using the MM/GBSA method to calculate their binding energies (Table 3). This sophisticated computational technique offers insights into the molecular interactions between ligands and the enzyme's active site, thus clarifying the stability and affinity of potential antidiabetic drug candidates.

The total binding energy (ΔE_{TOTAL}) for the acarbose system, a known inhibitor, was measured at -25.21 kJ/mol, reflecting the sum of van der Waals, electrostatic, and solvation interactions that contribute to the stability of the ligand-enzyme complex. In contrast,

(2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone exhibited a more negative binding energy of -33.86 kJ/mol, indicating a stronger affinity for α -glucosidase and suggesting more stable interactions. Methyl pyropheophorbide A displayed a slightly less negative binding energy of -24.60 kJ/mol.

To further understand the molecular interactions, we analyzed the individual energy components contributing to binding stability. The electrostatic energy (ΔE_{ELE}) for the acarbose system was -14.72 kJ/mol, indicating favorable interactions within the active site. Conversely, (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone, and methyl pyropheophorbide A had less negative electrostatic energies of -0.9 kJ/mol and -1.38 kJ/mol, respectively, suggesting net repulsion. Additionally, in Generalized Born energy (ΔE_{GB}), the polar contribution to solvation energy was -33.13 kJ/mol for the acarbose system, indicating less favorable solvation. In contrast, both *D. trifasciata* compounds exhibited more negative values of 10.16 kJ/mol and 9.55 kJ/mol, respectively, implying more favorable solvation effects when binding to α -glucosidase.

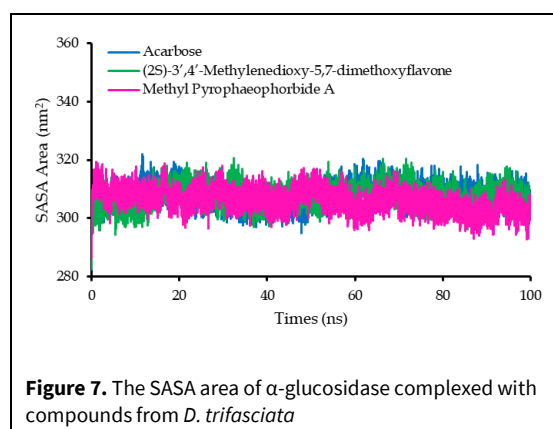
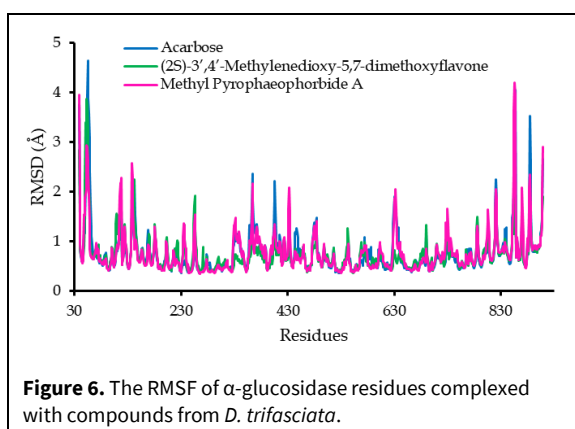
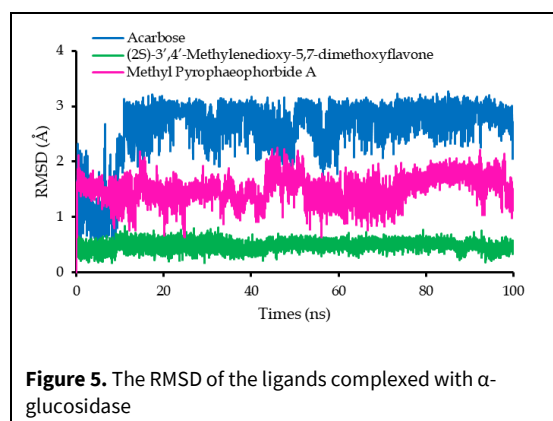
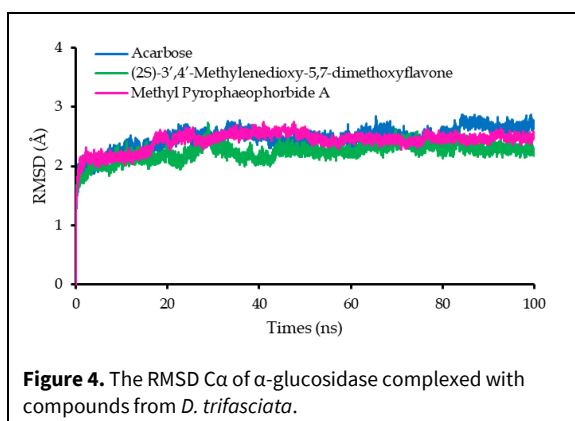


Table 3. The binding energies from MM/GBSA of α -glucosidase complex systems.

Alfa-glucosidase systems (kJ/mol)					
Compounds	ΔE_{VDW}	ΔE_{ELE}	ΔE_{GB}	ΔE_{SURF}	ΔE_{TOTAL}
Acarbose	-39.07	-14.72	33.13	-4.56	-25.21
Methyl pyropheophorbide A	-30.39	-0.90	10.16	-3.47	-24.60
(2S)-3',4'-Methylenedioxy-5,7-dimethoxyflavone	-38.04	-1.38	9.55	-4.00	-33.86

Table 4. ADME profiles of the identified compounds from the *Dracaena trifasciata* subfraction.

Compound	Log S (ESOL)	GI absorption	P-gp substrate	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
Methyl pyropheophorbide A	-4.71 (Moderate soluble)	High	Yes	No	No	Yes	No	No
(2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone	-3.77 (Soluble)	High	Yes	No	No	No	Yes	Yes

The van der Waals energy (ΔE_{VDW}) significantly facilitated binding, with (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone and methyl pyropheophorbide A showing highly negative values of -38.04 kJ/mol and -30.39 kJ/mol, respectively, indicating strong attractive interactions within the enzyme's hydrophobic pockets. These values were comparable to the acarbose system's van der Waals energy of -39.07 kJ/mol, suggesting that compounds from *D. trifasciata* form tight and stable interactions within the active site of α -glucosidase.

ADME properties

The analysis of the ADME properties of compounds from the *D. trifasciata* subfraction is presented in Table 4. Notably, (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone exhibited significant solubility, whereas methyl pyropheophorbide A was categorized as having moderate solubility. Solubility is a critical parameter in drug development as it determines the ability of a compound to dissolve in biological fluids and be absorbed by the body. This property highlights the potential of these compounds in drug development, as improved solubility can enhance their efficacy and facilitate progression through various stages, from formulation to successful absorption (Ottaviani et al., 2010; Ritchie et al., 2013). Furthermore, the chemical constituents of this subfraction demonstrated a high gastrointestinal (GI) absorption profile, indicating that these compounds could be efficiently absorbed through the gastrointestinal tract. This property likely contributes to their bioavailability and distribution throughout the body (Vinarov et al., 2021). However, predictive analysis suggests that both compounds are substrates of P-glycoprotein (P-gp). Compounds exhibiting P-gp substrate properties

are subject to active efflux transport, potentially leading to reduced absorption, limited distribution, and decreased therapeutic efficacy (Coluzzi et al., 2022).

Additionally, compounds from the *D. trifasciata* subfraction exhibited interactions with key enzymes in the cytochrome P450 (CYP) family. Methyl pyropheophorbide A was predicted to inhibit only CYP2C9, while (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone was predicted to inhibit CYP2D6 and CYP3A4 isoforms. These enzymes are essential for drug metabolism and elimination, and their inhibition can result in significant alterations in drug metabolism, potentially leading to elevated drug concentrations within the body (Hollenberg, 2002; Kirchmair et al., 2015).

Toxicity prediction

The toxicity profile analysis of compounds derived from the *D. trifasciata* subfraction, as presented in Table 5, provides critical insights into potential side effects, a key consideration in drug development. This analysis predicts toxicity based on criteria such as hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity. Compound methyl pyropheophorbide A is predicted to exhibit no toxicity under any of these criteria. In contrast, (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone is predicted to have carcinogenic and immunotoxic properties.

Hepatotoxicity refers to the potential for liver damage, which presents a significant challenge in drug development due to the liver's essential role in metabolism and detoxification (Rusyn et al., 2021). Carcinogenicity, the ability of a substance to induce cancer, is a critical concern in pharmaceutical research due to its severe implications for human health (Liu et

al., 2023). Similarly, mutagenicity denotes the ability to cause genetic mutations, potentially leading to hereditary effects (Rosendahl Huber et al., 2021). Immunotoxicity describes a compound's capacity to alter immune system function, either by suppression or overstimulation (Bou et al., 2021). Meanwhile, cytotoxicity reflects a compound's ability to damage or kill living cells, often through the disruption of cellular functions or membrane integrity (Fröhlich, 2013).

Understanding these toxicity profiles is vital in the drug development process, as it informs the selection of compounds, dosage optimization, and safety evaluations (Hughes et al., 2011). Comprehensive toxicity assessments, combined with strategies to mitigate associated risks, enable researchers to navigate the complexities of natural compound usage, optimizing therapeutic potential while minimizing adverse effects.

Drug likeness properties

The prediction of Lipinski's rule compliance for the compounds identified in the *D. trifasciata* subfraction is presented in Table 6. Notably, all compounds from this plant demonstrated properties that satisfied Lipinski's criteria. Lipinski's rules provide a foundational framework for assessing the potential of molecules to become orally active drugs, with a focus on key parameters such as solubility and absorption (Mermer and Vakal, 2021). Furthermore, the results of the Lipinski's property analysis identified the most promising compounds as potential candidates for oral drug development. These compounds exhibited enhanced bioavailability, thereby increasing their potential efficacy and safety when administered orally (Doak et al., 2014).

DISCUSSION

Currently, diabetes mellitus remains a prominent degenerative disease that necessitates prompt and effective management to attain optimal health and well-being. Consequently, ongoing research is being conducted to discover novel medications for diabetes mellitus. An area of emphasis in drug research involves using organic compounds to acquire molecules and predict pharmacological activity through both *in vitro* and *in silico* methods. One of the target molecules used for drug discovery and development is the α -glucosidase enzyme. Glycosidases are crucial enzymes involved in glucose metabolism. They can break down glucoside linkages through hydrolysis, resulting in the release of monosaccharides. α -glucosidase includes enzymes such as maltase, isomaltase, glucoamylase, and sucrase, which are anchored to the membrane of small intestinal epithelial cells. Inhibitors of α -glucosidase act as competitive inhibitors, interfering with the activity of small intestinal α -glucosidase, which results in delayed or reduced glucose absorption in the small intestine. Consequently, this mechanism effectively lowers blood glucose levels (Lu et al., 2023).

The ethyl acetate fractions (FE), subfraction C (SC), and subfraction E (SE) were tested at varying concentrations (100, 200, 300, 400, 500 μ g/mL). Among the samples, SE demonstrated the highest percentage of inhibition at a concentration of 500 μ g/mL, achieving a remarkable 75.17%. This was closely followed by FE and SC, with inhibition values of 70.11% and 69.89%, respectively. These findings are illustrated in Fig. 2, which visually underscores the significant inhibitory effect of SE compared to FE and SC.

Table 5. Prediction of the toxicity properties of the identified compounds from *Dracaena trifasciata* subfraction.

Compound	Hepatotoxicity (probability)	Carcinogenicity (probability)	Immunotoxicity (probability)	Mutagenicity (probability)	Cytotoxicity (probability)
Methyl pyropheophorbide A	Inactive (0.71)	Inactive (0.55)	Inactive (0.69)	Inactive (0.65)	Inactive (0.62)
(2S)-3',4'-Methylenedioxy-5,7-dimethoxyflavone	Inactive (0.77)	Active (0.57)	Active (0.98)	Inactive (0.63)	Inactive (0.9)

Table 6. Lipinski's rule estimation of identified compounds from *Dracaena trifasciata* subfraction.

Compound	Molecular weight	MLOGP	Num. H-bond acceptors	Num. H-bond donors	Lipinski rules
Methyl pyropheophorbide A	548.67	2.40	6	2	Yes; 1 violation: MW>500
(2S)-3',4'-Methylenedioxy-5,7-dimethoxyflavone	319.37	1.92	5	0	Yes; 0 violation

Molecular weight (criteria ≤ 500 g/mol), MLOGP (criteria $\text{Log } P_{\text{o/w}} \leq 4.15$); Number of hydrogen bond (H-bonds) acceptors (criteria ≤ 10); Number of hydrogen bond (H-bonds) donors (criteria ≤ 5).

The concentration required to inhibit 50% (IC_{50}) of the enzyme activity, a critical parameter in pharmacology indicating the efficacy of a compound, showed acarbose exhibited potent inhibition with an IC_{50} value of less than 50 $\mu\text{g/mL}$, consistent with its established role as an effective α -glucosidase inhibitor. In contrast, the tested samples exhibited varying levels of inhibitory potency. SE showed a strong inhibitory effect with an IC_{50} value ranging from 50 to 100 $\mu\text{g/mL}$, suggesting it has moderate potential as an α -glucosidase inhibitor. On the other hand, FE and SC exhibited weaker inhibitory effects with IC_{50} values greater than 151 $\mu\text{g/mL}$, indicating lower efficacy compared to both SE and acarbose.

The potential of FE, SC, and SE to inhibit α -glucosidase is attributed to their compound content. Our previous study identified the compound content of the subfractions of *D. trifasciata* using LC-MS/MS. The results showed that subfraction C contains alkaloid derivatives such as 1-acetyl- β -carboline and oliveramine, as well as the fatty acid derivative trichosanic acid. Subfraction E contains flavonoid derivatives, namely (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone, and alkaloid derivatives, namely methyl pyrophaeophorbide A (Kasmawati et al., 2022). Some compounds have been confirmed to possess antidiabetic properties. Research conducted *in vivo* has shown that flavonoid derivatives of 5,7-dimethoxyflavone can effectively decrease STZ-induced elevation in blood sugar and glycosylated hemoglobin. Additionally, these derivatives considerably raise the levels of C-peptide, insulin, hemoglobin, and total protein content (Xie et al., 2019). Furthermore, pheophorbide has been reported in various *in silico* studies to potentially modulate GLUT1 and be considered a lead for enhancing the GSIS pathway, thereby maintaining glucose homeostasis (Paul et al., 2024). The presence of 5,7-dimethoxyflavone and Pheophorbide A derivatives in subfraction E of *D. trifasciata* is thought to play a role in its antidiabetic activity. Similarly, subfraction C, which contains β -carboline derivatives, has been reported to inhibit the α -glucosidase enzyme (Xiao et al., 2023). Furthermore, the antidiabetic potential of this plant has also been reported in similar studies. An *in vitro* study demonstrated that the ethanol extract of *S. trifasciata* has the capacity to lower blood glucose levels, revealing an IC_{50} value of 158.31 $\mu\text{g/mL}$ against α -amylase (Anggia et al., 2019). Additionally, in another study, it was found that the ethanol extract of *S. trifasciata* administered to an alloxan-induced *Rattus norvegicus* model showed dose-dependent reductions in blood glucose levels (Lina et al., 2023).

Using computational studies, this research also examines the molecular mechanism of the compounds in the subfraction E of *D. trifasciata* against α -glucosidase. Comprehensive computational analysis and molecular docking studies have highlighted the potential of such compounds in interacting effectively with the active site of the α -glucosidase enzyme, thereby inhibiting its activity. Molecular docking and dynamics simulations provided deeper insights into the binding interactions and stability of the constituents of SE, specifically methyl pyrophaeophorbide A and (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone, with α -glucosidase. methyl pyrophaeophorbide A formed three hydrogen bonds with Ser505, Lys506, and Asn237, and engaged in hydrophobic interactions with Ile233, Phe236, Phe476, and Ala602, which significantly contributed to its binding stability. Meanwhile, (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone formed a hydrogen bond with Arg552 and hydrophobic interactions with Asp232, Trp329, Asp469, Asp568, and Phe601, effectively anchoring it within the enzyme's active site.

Building upon these interactions, stability analysis through molecular dynamics simulation revealed that the enzyme-compound complexes for both methyl pyrophaeophorbide A and (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone exhibited lower RMSD values compared to acarbose, indicating greater stability. The solvent-accessible surface area (SASA) analysis further supported these findings, showing similar stability profiles among the compounds, with (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone demonstrating exceptional stability. Further reinforcing the potential of these compounds, binding affinity analysis showed that (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone exhibited a more negative total binding energy (-33.86 kJ/mol) compared to acarbose (-25.21 kJ/mol), indicating stronger affinity and more stable interactions with α -glucosidase. The stability and binding affinity of this compound are crucial for the sustained inhibitory effect on α -glucosidase.

CONCLUSION

This study highlights the differential inhibitory effects of various fractions and subfractions from *D. trifasciata* Prain. on α -glucosidase activity, with subfraction E (SE) standing out as a particularly promising candidate for further investigation and development as an antidiabetic therapeutic agent due to its relatively strong inhibitory effect. However, its efficacy is still significantly lower than that of acarbose, indicating the need for further research to enhance its therapeutic potential. Both *in vitro* and computational findings collectively underscore the strong inhibitory

potential of SE from *D. trifasciata* against α -glucosidase. The robust binding interactions and stability of (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone from SE suggest its promise as an antidiabetic agent. Although the analysis concludes that methyl pyropheophorbide A exhibits a safer ADME profile and lower toxicity compared to (2S)-3',4'-methylenedioxy-5,7-dimethoxyflavone. These findings warrant further investigation and development to fully realize the therapeutic potential of these compounds in managing diabetes.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

The authors (H.K.) would like to thank Penelitian Kolaborasi Internasional Tahun 2024 from the Faculty of Pharmacy, Universitas Halu Oleo, under contract number 23a/UN29.18/KU/2024.

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AUTHOR CONTRIBUTION:

Contribution	Kamawati H	Ruslin R	Arfan A	A.Sida N	Wibowo A	Hanafiah MAKM	Yahya MFM
Concepts or ideas	x	x			x	x	x
Design	x	x	x	x			
Definition of intellectual content	x	x			x	x	x
Literature search	x		x	x			
Experimental studies			x	x			
Data acquisition	x		x	x			
Data analysis	x		x	x			
Statistical analysis			x	x			
Manuscript preparation			x	x			
Manuscript editing	x	x			x	x	x
Manuscript review	x	x	x	x	x	x	x

Citation Format: Kamawati H, Ruslin R, Arfan A, A.Sida N, Wibowo A, Hanafiah MAKM, Yahya MFM (2025) In-depth insights into the antidiabetic activity of *Dracaena trifasciata* (Prain) Mabb. fractions and subfractions: *In vitro* and computational studies. *J Pharm Pharmacogn Res* 13(s1): S13–S26. https://doi.org/10.56499/jppres24.2193_13.s1.13

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