Comparative Computational Screening of α-, β-, and γ-Mangostin Targeting *Scytalone Dehydratase* in *Pyricularia oryzae* for Sustainable Rice Production in Indonesia

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ABSTRACT

Rice productivity in Indonesia faces serious threats from rice blast disease caused by Pyricularia oryzae. This study evaluates and compares the potential of α-, β-, and γ-mangostin as Scytalone Dehydratase (SDH) inhibitors using a molecular docking and physicochemical profiling approach. Molecular docking simulations via PyRx revealed that α-, γ-, and β-mangostin exhibited binding affinities of -7.3, -7.2, and -6.9 kcal/mol, respectively. Interaction analysis showed that α- and γ-mangostin established more favorable interactions within the active site of the SDH enzyme. SwissADME evaluation indicated that all isomers possess generally favorable physicochemical properties despite poor water solubility. These findings identify α- and γ-mangostin as promising inhibitor candidates, supporting the development of environmentally friendly biofungicides for sustainable rice blast management in Indonesia.

ABSTRAK

Produktivitas padi di Indonesia menghadapi ancaman serius dari penyakit blas yang disebabkan oleh Pyricularia oryzae. Penelitian ini mengevaluasi dan membandingkan potensi α-, β-, and γ-mangostin sebagai inhibitor Scytalone Dehydratase (SDH) menggunakan pendekatan penambatan molekuler (molecular docking) dan profil fisikokimia. Simulasi penambatan molekuler melalui PyRx menunjukkan bahwa α-, γ-, and β-mangostin masing-masing memiliki binding affinity sebesar -7,3, -7,2, dan -6,9 kcal/mol. Analisis interaksi mengungkapkan bahwa α- and γ-mangostin membentuk interaksi yang lebih optimal pada sisi aktif enzim SDH. Evaluasi SwissADME menunjukkan bahwa seluruh isomer memiliki sifat fisikokimia yang baik meskipun kelarutannya dalam air tergolong rendah. Temuan ini mengidentifikasi α- and γ-mangostin sebagai kandidat inhibitor potensial guna mendukung pengembangan biofungisida ramah lingkungan untuk pengendalian penyakit blas padi di Indonesia.

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INTRODUCTION

Rice *(Oryza sativa* L.*)* is a strategic food commodity that serves as a staple for more than half of the global population, including the people of Indonesia. As a nation with high rice consumption, sustainable rice production plays a crucial role in maintaining national food security, meeting public consumption needs, and supporting agricultural sector growth. According to Statistics Indonesia (BPS), Indonesia's rice production in 2025 is projected to reach 71.95 million tons of harvested dry grain and 60.21 million tons of milled dry grain, with a harvested area of 11.32 million hectares. Meanwhile, rice production intended for human consumption in 2025 is estimated at 34.69 million tons, an increase of 4.07 million tons (13.29%) compared to 2024. However, this rise in production does not guarantee the sustainability of national food security, as rice productivity faces various threats, including plant

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diseases that can cause significant crop failure. Therefore, controlling rice plant diseases is essential for maintaining production stability and ensuring the availability of rice for the population.

Pyricularia oryzae is a pathogen that causes significant damage to rice crops. This fungus causes rice blast disease, which can attack nodes, the neck of the plant, leaf collars, and even the grain itself, ultimately reducing both the quality and quantity of the harvest. Symptoms manifest as diamond-shaped spots with pointed ends; the centers are gray, while the margins range from brown to reddish-brown (Kusumawati & Istiqomah). The pathogen spreads via conidia carried by wind or water splashes, particularly under environmental conditions characterized by high humidity and temperatures conducive to fungal development. The disease affects 12% of the total rice cultivation area in Indonesia annually, with a potential yield loss of up to 90% in susceptible varieties (Dagsy *et al.*, 2025). Jayasanti *et al.* (2026) report that rice blast has been widely observed affecting rice crops in several Indonesian regions, including West Sumatra, South Sulawesi, Lampung, South Sumatra, Kalimantan, West Java, and Bali, and was identified as a cause of a 10% decline in rice production in Gianyar Regency in 2023.

Successful infection by *P. oryzae* relies heavily on the formation of an appressorium, a specialized structure that enables the fungus to penetrate plant tissues. The appressorium generates immense turgor pressure, which is required to breach the plant cell wall (Qu *et al.*, 2022). Melanin plays a crucial role in the infection process by reinforcing the appressorium wall, thereby facilitating the generation of sufficient turgor pressure for plant penetration. The melanin biosynthesis pathway in *P. oryzae* involves several enzymes, one of which is Scytalone Dehydratase (SDH). SDH is a key enzyme in the 1,8-dihydroxynaphthalene (DHN)-based melanin biosynthesis pathway (Motoyama et al., 2022). Inhibiting SDH disrupts melanin production, which in turn impairs the fungus's ability to form appressoria, the specialized structures necessary for penetrating plant tissues. This disruption can effectively reduce the fungus's capacity to infect and cause disease in plants such as rice, which is highly susceptible to rice blast disease caused by *P. oryzae*.

Rice blast disease caused by *Pyricularia oryzae* remains one of the major constraints in rice cultivation, and its management is still predominantly dependent on the application of synthetic fungicides, such as tricyclazole, azoxystrobin, tebuconazole, isoprothiolane, and kasugamycin. Shi *et al.* (2024) reported that these fungicides effectively suppress the development of *P. oryzae* through various mechanisms, including the inhibition of melanin biosynthesis, mitochondrial respiration, and ergosterol biosynthesis. However, the continuous use of synthetic fungicides may increase the selection pressure on pathogen populations, leading to the emergence of fungicide-resistant isolates, while also leaving residues that may adversely affect the environment and non-target organisms (D'Avila *et al.*, 2021). Therefore, alternative disease management strategies that are safer, more effective, and environmentally friendly are urgently needed, particularly through the utilization of natural bioactive compounds as potential biofungicides.

One promising source of natural bioactive compounds for biofungicide development is the pericarp of mangosteen (Garcinia mangostana L.), which is rich in xanthone derivatives, particularly a-, B-, and y-mangostin (Chen et al., 2018).These mangostin isomers have been widely reported to exhibit antifungal activity, highlighting their potential as natural agents for plant disease control. One of the most promising molecular targets for controlling *Pyricularia oryzae* is the enzyme Scytalone Dehydratase (SDH), which plays a crucial role in the melanin biosynthesis pathway. Melanin is an essential component in the formation of the appressorium, enabling the fungus to generate sufficient turgor pressure to penetrate host plant tissues.

Consequently, inhibition of the SDH enzyme may disrupt melanin biosynthesis and reduce the pathogenicity of *P. oryzae*, making α-, β-, and γ-mangostin attractive candidates as SDH inhibitors for the development of environmentally friendly biofungicides (Motoyama *et al.*, 2021).

The potential of a-, β-, and y-mangostin as biofungicide candidates warrants further investigation to elucidate the molecular mechanisms underlying their antifungal activity. Although the antifungal properties of mangostin have been extensively reported against various fungal pathogens, studies comparing the computational inhibitory potential of a-, β-, and y-mangostin against the Scytalone Dehydratase (SDH) enzyme in *Pyricularia oryzae* remain limited. Hasan et al. (2022) demonstrated that molecular docking is an effective approach for identifying natural compounds as potential inhibitors of target proteins in P. *oryzae*; however, their study did not evaluate or compare the binding affinity and interaction profiles of the three mangostin isomers toward SDH. Evaluating these compounds through a computational approach prior to laboratory experiments (in vitro or in vivo) is highly necessary. This approach serves as a rapid and cost-effective preliminary screening, providing crucial insights into the specific molecular interactions and binding mechanisms at the atomic level, which cannot be directly observed through conventional laboratory testing. Therefore, this study aims to evaluate and compare the potential of a-, ß-, and y-mangostin as SDH inhibitor candidates, thereby providing a scientific basis for the development of environmentally friendly biofungicides.

Based on this research gap, the present study employed a molecular docking approach to evaluate the potential of a-, β-, and y-mangostin as inhibitors of the Scytalone Dehydratase (SDH) enzyme in *Pyricularia oryzae*. Pinzi and Rastelli (2019) explained that molecular docking is a computational method capable of rapidly, efficiently, and cost-

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effectively predicting the binding affinity and interaction patterns between ligands and target proteins, making it a valuable tool for the preliminary screening of potential inhibitors prior to in vitro and in vivo validation. To complement the docking analysis, it is essential to determine whether these compounds are not only effective but also safe for practical use. Therefore, their physicochemical properties, along with broader ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiles and specific toxicity endpoints, were evaluated using predictive tools such as SwissADME and pkCSM. This comprehensive prediction provides vital information regarding their molecular characteristics, environmental safety, and overall suitability as environmentally friendly biofungicide candidates.

METHODS

This study employed a quantitative approach using an *in silico* experimental method (computational screening) through molecular docking modeling. This approach was applied to evaluate the potential of α-, β-, and γ-mangostin compounds as specific inhibitor candidates against the *Scytalone Dehydratase* (SDH) enzyme in the fungus *Pyricularia oryzae*.

Research Data Sources

The data used in this computational study were obtained entirely from valid international databases of macromolecules and chemical compounds, including:

Target Protein (Receptor)

The three-dimensional structure of the Scytalone Dehydratase (SDH1) enzyme from the Magnaporthe/*Pyricularia oryzae* macromolecule was obtained from the RCSB Protein Data Bank (PDB) (https://www.rcsb.org/) with PDB ID 1STD. This structure was selected based on its experimental resolution of 2.90 Å.

Test Compounds (Ligands)

The three-dimensional structures of the mangostin isomers namely, α-mangostin, β-mangostin, and γ-mangostin were downloaded from the PubChem chemical database. The data extracted from this database included the official IUPAC names, molecular formulas, and Simplified Molecular-Input Line-Entry System (SMILES) data formats for these three xanthone compounds.

Molecular Preparation and Molecular Docking Process

1. Protein preparation using BIOVIA Discovery Studio by removing water molecules and nonspecific heteroatom components, and adding polar hydrogen atoms.
2. Ligand preparation by converting the original SDF format into a 3D PDB format, then reopening the file to add polar hydrogen atoms.
3. File optimization by converting the protein to PDBQT format and performing energy minimization on the ligand before converting it to PDBQT format.
4. Docking simulation using AutoDock Vina by maximizing the search space coordinates (grid box) on the target protein.
5. Extract results by selecting the best ligand conformation and exporting it as a single protein-ligand complex file in PDB format
6. Visualize and analyze the results by examining the 3D geometric positions and mapping the types of intermolecular interactions and key amino acid residues in the form of 2D diagrams. Additional Analysis (Physicochemical and Pharmacokinetic Properties)

Analysis Parameters

The evaluation of molecular docking results is based on four main parameters:

1. Binding Affinity: Binding free energy (kcal/mol) as scored by Vina, where a larger negative value indicates a stronger and more stable bond.
2. RMSD (Root Mean Square Deviation): A validation parameter for ligand position coordinates to ensure that the resulting conformational poses fall within a valid tolerance range.
3. Amino Acid Residue Specificity: Mapping the involvement of functional amino acid residues at the protein's active site that interact directly with the test compound. 4. MM-GBSA Calculation and Interaction Distance: Estimation of the binding free energy using the MM-GBSA method to validate docking stability, and measurement of interaction distances (e.g., hydrogen bond lengths in Å) to evaluate the strength and specificity of the intermolecular bonds.

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Additional Analysis (Physicochemical and Pharmacokinetic Properties)

To evaluate the suitability of ligands as safe biofungicide active ingredient candidates, predictive analyses of physicochemical properties (such as solubility and lipophilicity/logP) and ADMET profiles (Absorption, Distribution, Metabolism, Excretion, and Toxicity) were conducted. These analyses were performed computationally based on the ligand's SMILES structure using predictive platforms such as SwissADME for physicochemical characterization and pkCSM for broader ADMET and specific toxicity endpoints.

RESULTS AND DISCUSSIONS

Molecular docking is a computational approach widely used in the drug discovery process to predict the binding affinity between a target protein and a ligand molecule. Binding affinity reflects the strength and stability of the interaction between the ligand and the target protein and is commonly expressed as an estimated binding free energy. Docking simulations are performed within a predefined search space (*grid box*), which restricts ligand movement and directs the docking process toward the active site of the target protein (Weni et al., 2020). The simulation generates multiple binding poses, each representing a distinct ligand conformation with a corresponding binding affinity value. In addition to predicting binding affinity, molecular docking provides information regarding the orientation of the ligand within the binding pocket and the molecular interactions formed between the ligand and amino acid residues at the protein's active site, including hydrogen bonds, hydrophobic interactions, and electrostatic interactions (Putri et al., 2024).

As illustrated in the 2D interaction analysis (Figures 1.1, 1.2, and 1.3), each isomer displays a distinct binding orientation and interaction pattern within the SDH active site. Figure 1.1 reveals that a-mangostin fits optimally into the binding pocket, stabilized by crucial conventional hydrogen bonds and extensive π-alkyl networks with key residues. In contrast, β-mangostin (Figure 1.2) exhibits an unfavorable donor-donor interaction (marked in red) and fewer stabilizing hydrogen bonds, which structurally explains its weakest binding affinity among the three. Meanwhile, γ-mangostin (Figure 1.3) displays a highly similar binding mode to a-mangostin, maintaining key hydrogen bonds with essential residues like HIS A:128 and TRP A:153, corroborating its highly competitive affinity score.

Figure 1.1. Molecular docking results of 1STD with α-mangostin: (A) docking grid box (PyRx), (B) protein–ligand complex (PyMOL), and (C) chemical structure of α-mangostin

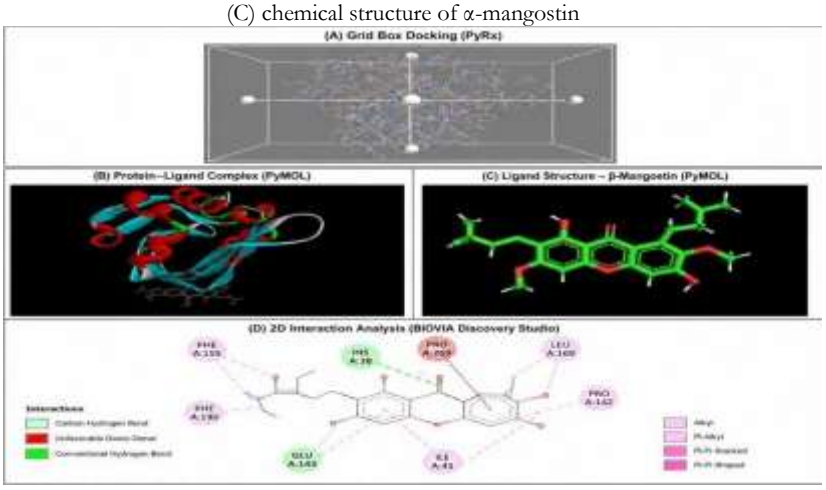
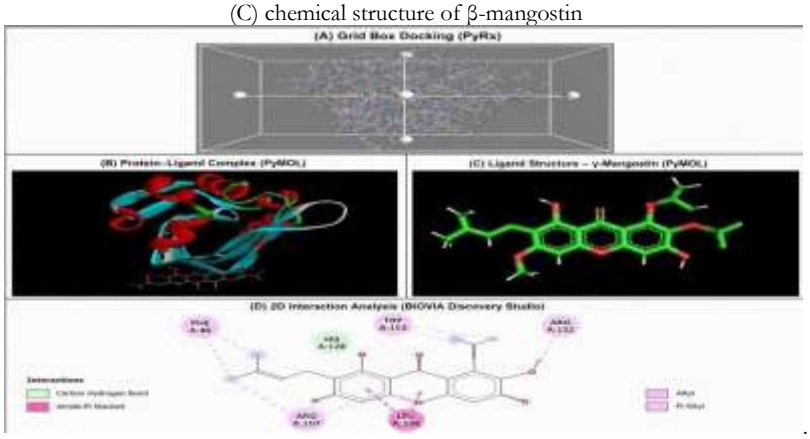


Figure 1.2. Molecular docking results of 1STD with β-mangostin: (A) docking grid box (PyRx), (B) protein–ligand complex (PyMOL), and (C) chemical structure of β-mangostin



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Figure 1.3. Molecular docking results of 1STD with γ-mangostin: (A) docking grid box (PyRx), (B) protein–ligand complex (PyMOL), and (C) chemical structure of γ-mangostin.

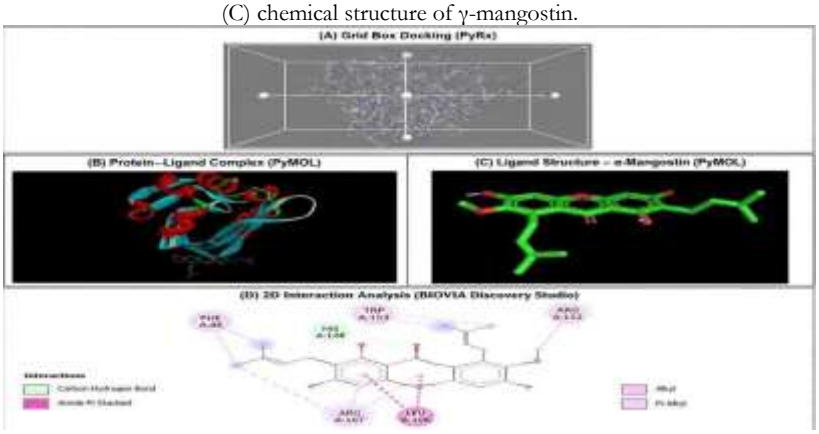


Table 1. Molecular docking parameters of α-, β-, and γ-mangostin, including binding affinity, RMSD, interacting amino acid residues, hydrogen bond interactions, and hydrophobic interactions, as determined using PyRx and BIOVIA Discovery Studio

Protein Target	Ligand	Binding Affinity	RMSD lower	RMSD upper	Amino Acid Residue	Hydrogen Bond	Hydrophobic
1STD	α-mangostin	-7,3	1.916	8.206	TRP A: 153; ARG A: 152; HIS A: 128; PHE A: 86; ARG A: 107; LEU A: 106	1 Conventional; 1 Carbon	2 Amide-Pi; 2 Alkyl; 5 Pi-Alkyl; 1 Pi-Sigma; 1 Pi-Pi T Shaped;
	β-mangostin	-6,5	1.478	2.166	TRP A: 153; PHE A: 86; ARG A: 107; HIS A: 128; ARG A: 152; ALA A: 130	1 Carbon; 3 Alkyl; 4 Pi-Alkyl	
γ-mangostin	-7,2	2.187	8.039	TRP A: 153; HIS A: 128; LEU A: 106; ARG A: 107;	1 Conventional; 1 Carbon	2 Amide-Pi; 5 Pi-Alkyl	

The molecular docking simulation between the target protein 1STD, representing the Scytalone Dehydratase (SDH) enzyme from *Pyricularia oryzae*, and α-mangostin yielded a binding affinity of −7.3 kcal/mol, with a lower RMSD value of 1.916 Å, indicating high docking reliability. α-Mangostin was predicted to interact with the amino acid residues TRP A:153, ARG A:152, HIS A:128, PHE A:86, ARG A:107, and LEU A:106 through a combination of hydrogen bonds and hydrophobic interactions. The hydrogen bonds consisted of one conventional hydrogen bond and one carbon hydrogen bond, whereas the hydrophobic interactions comprised two amide–π interactions, two alkyl interactions, and five π–alkyl interactions.

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In contrast, β-mangostin exhibited a lower binding affinity toward the same target protein (1STD), with a value of −6.5 kcal/mol and a lower RMSD of 1.478 Å, indicating a highly reliable docking pose. β-Mangostin was predicted to interact with the amino acid residues TRP A:153, PHE A:86, ARG A:107, HIS A:128, ARG A:152, and ALA A:130. The interaction profile included one carbon hydrogen bond, one π–sigma interaction, one π–π T-shaped interaction, three alkyl interactions, and four π–alkyl interactions.

γ-Mangostin exhibited a binding affinity of −7.2 kcal/mol, while its lower RMSD value was 2.187 Å, indicating a reasonably reliable docking pose. Although this value suggests a slight deviation from the best docking conformation, the predicted pose remains highly similar and acceptable for further analysis. γ-Mangostin was predicted to interact with the amino acid residues TRP A:153, HIS A:128, LEU A:106, ARG A:107, and PHE A:86. The hydrogen bonding interactions consisted of one conventional hydrogen bond and one carbon hydrogen bond, whereas the hydrophobic interactions included two amide–π interactions and five π–alkyl interactions.

The docking pose with the lowest root-mean-square deviation (RMSD) was selected to represent the binding interaction between the test ligand and the target protein. The docking results demonstrated good agreement between the predicted ligand conformations, as indicated by RMSD values of ≤ 2 Å. A more negative binding affinity value indicates a stronger binding affinity between the ligand and the receptor, whereas a less negative (or higher) binding affinity value reflects weaker binding interactions (Nugroho & Fauzi, 2024).

Based on the molecular docking results presented in Table 1, α-mangostin exhibited the most favorable binding affinity, with a value of −7.3 kcal/mol, and demonstrated high docking reliability, as evidenced by a lower RMSD value of ≤ 2 Å. γ-Mangostin showed a slightly less favorable binding affinity of −7.2 kcal/mol, differing by only 0.1 kcal/mol from α-mangostin. However, its lower RMSD value exceeded 2 Å, indicating that although the predicted docking pose remained acceptable, it was less accurate than that of α-mangostin. In contrast, β-mangostin produced the most accurate docking pose, with the lowest RMSD value (1.478 Å). Nevertheless, it exhibited the weakest binding affinity (−6.5 kcal/mol) among the three ligands evaluated.

The differences in binding affinity among the compounds are likely attributed to structural variations in α-, β-, and γ-mangostin, which influence their binding orientation, the type and number of interactions with protein residues, and the overall fit of each ligand within the Scytalone Dehydratase (SDH) binding pocket (Pantsar & Poso, 2018). However, the observed differences in binding affinity cannot be explained solely by the number of interactions formed. This is evident from β-mangostin, which exhibited a greater number of hydrophobic interactions than both α- and γ-mangostin, yet produced a less favorable binding affinity. These findings suggest that the energetic contribution and quality of individual interactions play a more critical role than the total number of interactions. In molecular docking, the scoring function estimates the overall binding energy by integrating the energetic contributions of multiple non-covalent interactions, including hydrogen bonds and hydrophobic interactions. Consequently, the predicted binding affinity reflects the cumulative effect of all interaction energies rather than being determined solely by the number of interactions formed

Although molecular docking is capable of predicting the binding affinity between a ligand and its target protein, the evaluation of physicochemical properties remains necessary to provide additional information regarding molecular characteristics that support the interpretation of docking results. Therefore, physicochemical characterization was performed as a complementary analysis to evaluate the molecular characteristics of α-, β-, and γ-mangostin as potential inhibitors of the Scytalone Dehydratase (SDH) enzyme. Using the SwissADME platform, several physicochemical parameters, including molecular weight, lipophilicity (LogP), and water solubility, were computationally predicted to provide an overview of the characteristics of each mangostin isomer. These parameters were used as supporting data to evaluate the potential of α-, β-, and γ-mangostin as biofungicide candidates for controlling rice blast disease caused by *Pyricularia oryzae* (Daina et al., 2017).

Table 2 presents the predicted physicochemical properties of α-, β-, and γ-mangostin generated using SwissADME. The analyzed parameters included molecular formula, molecular weight, lipophilicity (XLOGP3), water solubility, and Lipinski's Rule of Five. These parameters were selected because they provide information regarding molecular size, lipophilic characteristics, aqueous solubility, and the suitability of compounds as bioactive molecules. Overall, the three mangostin isomers exhibited relatively similar physicochemical characteristics; however, several differences were observed in specific parameters that may influence the properties of each compound.

Table 2. Predicted physicochemical properties of α-, β-, and γ-mangostin using SwissADME

Parameter	α-Mangostin	β-Mangostin	γ-Mangostin
Molecular Formula	$C_{24}H_{26}O_6$	$C_{25}H_{28}O_6$	$C_{24}H_{26}O_6$
Molecular Weight (g/mol)	396,43	424,49	396,43

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Lipophilicity (XLOGP3)	6.49	7.14	6.49
Water Solubility	Poorly soluble	Poorly soluble	Poorly soluble
Lipinski Violations	1	1	1

Based on the SwissADME analysis presented in Table 2, α-, β-, and γ-mangostin exhibited relatively similar physicochemical characteristics. All three isomers were predicted to be poorly soluble in water but differed in terms of molecular formula, molecular weight, and lipophilicity (LogP). These differences are likely associated with variations in the functional group arrangement among the mangostin isomers, which may influence their physicochemical properties. These parameters are important because they are related to molecular size, hydrophobicity, and other physicochemical characteristics that support the interpretation of molecular docking results. Therefore, each parameter was further discussed to evaluate the potential of α-, β-, and γ-mangostin as biofungicide candidates against *Pyricularia oryzae*.

Differences in molecular weight were observed among the three mangostin isomers, with α- and γ-mangostin having an identical molecular weight of 396.43 g/mol, whereas β-mangostin exhibited a higher molecular weight of 424.49 g/mol (Table 2). This difference indicates that β-mangostin possesses a slightly larger molecular size than α- and γ-mangostin due to structural variations among the isomers. Molecular weight is an important physicochemical parameter that may influence the characteristics of a compound, including molecular size, diffusion ability, distribution, and the tendency to initiate interactions with biological targets (Daina et al., 2017). However, molecular weight alone cannot be considered a definitive indicator of biological activity because molecular performance is also influenced by other physicochemical properties and structural features that determine the interaction pattern with the target protein (Pinzi & Rastelli, 2021). Therefore, molecular weight should be interpreted together with other physicochemical parameters to provide a more comprehensive understanding of the characteristics of α-, β-, and γ-mangostin as potential biofungicide candidates.

The lipophilicity parameter (XLOGP3) indicated that β-mangostin exhibited the highest LogP value (**7**.14), whereas both α- and γ-mangostin showed identical LogP values of 6.49 (Table 2). The LogP value represents the lipophilic nature of a compound or its tendency to partition into the lipid phase rather than the aqueous phase (Daina et al., 2017). The higher LogP value of β-mangostin suggests that this isomer is more hydrophobic than α- and γ-mangostin. Such hydrophobicity may facilitate interactions with nonpolar environments, including protein binding pockets that are commonly composed of hydrophobic amino acid residues. Nevertheless, lipophilicity alone is insufficient to determine the inhibitory potential of a compound because binding effectiveness is also influenced by molecular structure and its compatibility with the protein active site (Pinzi & Rastelli, 2021). Therefore, the LogP value should be considered as one of several supporting parameters for evaluating the physicochemical characteristics of α-, β-, and γ-mangostin.

All three mangostin isomers exhibited the same predicted water solubility classification, namely poorly soluble, according to the SwissADME analysis (Table 2). Water solubility describes the ability of a compound to dissolve in water and represents an important physicochemical property because it may influence formulation characteristics, stability, and compound distribution during application (Daina et al., 2017). These findings indicate that structural variations among α-, β-, and γ-mangostin do not substantially affect their aqueous solubility. The limited solubility of the three isomers is likely associated with the lipophilic nature of xanthone derivatives, as reflected by their relatively high LogP values. Nevertheless, poor water solubility does not necessarily diminish the biological potential of a compound; rather, it represents an important consideration for formulation development. Consequently, appropriate formulation strategies are required to improve compound dispersion and enhance application performance under field conditions (Pinzi & Rastelli, 2021).

Overall, the SwissADME analysis demonstrated that α-, β-, and γ-mangostin possess relatively favorable physicochemical characteristics as potential biofungicide candidates. The primary differences among the three isomers were observed in molecular weight and lipophilicity, whereas all compounds were predicted to exhibit low water solubility. Physicochemical properties constitute an important aspect in the development of bioactive compounds because they can influence molecular stability, formulation, and overall performance during practical application (Daina et al., 2017). Based on these findings, all three mangostin isomers remain promising candidates for development as natural biofungicides. However, their limited water solubility suggests that formulation optimization should be considered in future studies to improve their stability, dispersion, and application effectiveness, potentially through approaches such as nanoencapsulation or controlled-release delivery systems (Pinzi & Rastelli, 2021).

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Integrated Assessment of α-, β-, and γ-Mangostin as Potential Biofungicide Candidates

The present study demonstrated that the three mangostin isomers exhibited different inhibitory potentials against Scytalone Dehydratase (SDH), despite sharing the same xanthone backbone. Based on the molecular docking analysis, α-mangostin showed the strongest binding affinity (−7.3 kcal/mol), followed by γ-mangostin (−7.2 kcal/mol) and β-mangostin (−6.5 kcal/mol). Although β-mangostin produced the lowest RMSD value, indicating a highly reliable docking pose, its binding affinity remained lower than those of α- and γ-mangostin. These findings indicate that docking reliability alone does not necessarily correspond to stronger inhibitory activity, since the stability of the ligand–protein complex is also influenced by the quality and energetic contribution of molecular interactions rather than by RMSD alone.

The protein–ligand interaction analysis further supports this observation. α-Mangostin formed a balanced interaction profile consisting of conventional hydrogen bonds, carbon hydrogen bonds, amide–π interactions, alkyl interactions, and π–alkyl interactions with several amino acid residues within the SDH binding pocket. Hydrogen bonds are generally responsible for interaction specificity, whereas hydrophobic interactions contribute substantially to complex stabilization by lowering the binding free energy. Therefore, the stronger binding affinity observed for α-mangostin is likely associated with a more favorable interaction geometry and energetic contribution rather than simply a greater number of intermolecular contacts (Pinzi & Rastelli, 2021; Pantsar & Poso, 2018).

These molecular docking results are consistent with the physicochemical characterization predicted by SwissADME. All three mangostin isomers fulfilled the major drug-likeness criteria, including the Lipinski, Ghose, Veber, and Egan rules, indicating favorable molecular characteristics for bioactive compounds. Nevertheless, β-mangostin exhibited a higher molecular weight and lipophilicity than α- and γ-mangostin, whereas all three compounds showed relatively low aqueous solubility. These findings suggest that the physicochemical properties of mangostin isomers remain suitable for molecular interaction with SDH, although formulation strategies may be required to improve their dispersion and stability under practical agricultural conditions.

By integrating the molecular docking and SwissADME analyses, α-mangostin can be considered the most promising candidate among the three evaluated isomers. This compound demonstrated the strongest binding affinity while maintaining favorable physicochemical characteristics and acceptable molecular flexibility. Although γ-mangostin exhibited comparable docking performance, its overall interaction profile was slightly less favorable than that of α-mangostin. In contrast, β-mangostin displayed the weakest binding affinity despite producing the most reproducible docking pose. These findings emphasize that the selection of potential inhibitors should consider both molecular interaction quality and physicochemical properties rather than relying solely on docking accuracy.

The results obtained in this study are consistent with previous reports describing α-mangostin as a potent natural antifungal compound. Earlier studies have demonstrated that α-mangostin inhibits fungal growth through disruption of membrane integrity and interference with essential metabolic pathways. Although computational studies targeting Scytalone Dehydratase remain limited, the present findings provide additional evidence supporting the potential of α-mangostin as an inhibitor of fungal melanin biosynthesis, thereby contributing to the development of environmentally friendly alternatives to synthetic fungicides.

Despite these promising computational findings, the relatively poor water solubility predicted for all mangostin isomers may limit their practical application in agricultural systems. Therefore, future studies should focus on formulation approaches such as nanoencapsulation, controlled-release delivery systems, or biodegradable nanocarriers to improve solubility, stability, and field performance. Experimental validation through in vitro and in vivo assays is also necessary to confirm the inhibitory activity predicted by molecular docking and to evaluate the effectiveness of α-mangostin as a sustainable biofungicide for controlling rice blast disease.

CONCLUSIONS

This study demonstrated the potential of a-, β-, and y-mangostin as natural inhibitors of Scytalone Dehydratase (SDH), a key enzyme involved in melanin biosynthesis in *Pyricularia oryzae*. Molecular docking analysis revealed that a-mangostin exhibited the strongest binding affinity toward SDH, followed by y-mangostin and β-mangostin. Protein-ligand interaction analysis further indicated that the superior binding performance of a-mangostin was supported by favorable hydrogen-bonding and hydrophobic interactions within the active site of the target protein. Physicochemical characterization using SwissADME showed that all three mangostin isomers possessed generally favorable physicochemical properties, although their predicted water solubility was relatively low. Overall, the integration of molecular docking, protein-ligand interaction analysis, and physicochemical characterization identified a-mangostin as the most promising biofungicide candidate among the evaluated isomers. To address its relatively low aqueous solubility, future studies should explore formulation strategies such as nanoencapsulation to improve its stability and application efficiency, thereby supporting the development of environmentally friendly biofungicides for sustainable rice disease management.

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