Molecular Docking-Based Screening of Phenylpropanoids as Potential Antifungal Agents Against *Magnaporthe oryzae*

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Abstract

Background: Rice blast disease caused by *Magnaporthe oryzae* leads to annual yield losses of 10–30%, exacerbated by fungicide resistance and environmental toxicity of synthetic chemicals. Phenylpropanoids have shown potential as eco-friendly antifungal agents, yet systematic molecular screening against key pathogenic targets remains limited. **Aim:** This study aimed to identify potential phenylpropanoid-based antifungal compounds targeting Isocitrate Lyase (ICL1) and MoErs1 proteins of M. oryzae through an in silico approach. **Methods:** A total of 317 phenylpropanoid-derived ligands were screened using molecular docking against ICL1 (PDB ID: 5e9f) and MoErs1 (PDB ID: 7vs2). Docking simulations were conducted using AutoDock Vina, followed by interaction analysis using LigPlot+ and PLIP to evaluate binding affinity and interaction patterns. **Results:** Six compounds, Vitisin A, Miyabenol A, Viniferol D, Suffruticosol A, Suffruticosol B, and Isohopeaphenol, demonstrated superior binding affinity (up to −11.57 kcal/mol) compared to commercial fungicides Edifenphos and Tricyclazole. These ligands formed stable complexes through hydrogen bonding, hydrophobic interactions, and π-stacking with key active-site residues of both target proteins. **Conclusion:** These findings suggest that selected phenylpropanoids have strong potential as multi-target antifungal agents against M. oryzae. This study provides a structural foundation for developing environmentally friendly biofungicides and contributes to sustainable crop protection strategies, although further experimental validation is required.

Keywords: phenylpropanoid compounds; antifungal agents; rice blast disease; in silico screening; plant-derived metabolites

1. Introduction

Rice (*Oryza sativa*) is one of the world's most important food crops and a staple food for the human population, particularly in Asia (Devanna et al., 2022; Jiang et al., 2020; Yang et al., 2024). In the 2025–2026 crop year, global rice production is projected to reach a record 556.4 million metric tons, reflecting a steady upward trend driven by rising demand in rapidly developing economies (FAO, 2026; USDA, 2026). Furthermore, rice is a source of income and employment for millions of people. Since 2000, global rice consumption has continued to soar, making stable rice production increasingly crucial. Any disruption to crop yields can threaten global food security and economic stability.

However, the stability of this vital supply chain is increasingly threatened by biotic stressors. Among these, rice blast disease, caused by the fungus *Magnaporthe oryzae* (syn. *Pyricularia oryzae*), is a major threat to rice crops. This disease is the most destructive fungal disease globally, causing yield losses of 10-30% per year and even reaching 100% under severe environmental conditions (Cai et al., 2026; Liu et al., 2024). The pathogen *Magnaporthe oryzae* can infect rice at all stages of development and attack various plant parts, including leaves, stems, nodes, panicles, and roots (Devanna et al., 2022; Xun et al., 2023). *M. oryzae* possesses remarkable genomic plasticity, allowing it to rapidly evolve into new races. This often causes initially resistant rice varieties to become susceptible again within a short period of time in the field (Devanna et al., 2022).

The *M. oryzae* infection process begins when conidia attach to the rice leaf cuticle and germinate to form a germ tube, which then differentiate into a specialized dome-

shaped structure called an appressorium (Devanna et al., 2022; Liu et al., 2024). A distinctive melanin layer within the appressorium facilitates the accumulation of extremely high turgor pressure, which is then converted into mechanical force through penetration pegs to penetrate the host cuticle (Devanna et al., 2022; Liu et al., 2024) To further facilitate invasion, the fungus secretes a number of extracellular enzymes, such as cutinases, and effector proteins that suppress the host immune response (D. Wang et al., 2024). This pathogen can infect rice at all developmental stages and attack various plant parts, including leaves, stems, nodes, panicles, and roots. M. oryzae possesses remarkable genomic plasticity, allowing it to rapidly evolve into new races. This often causes initially resistant rice varieties to become susceptible again within a short time in the field (Devanna et al., 2022).

Current fungicides are inadequate to sustainably manage blast disease for several key reasons. First, the extensive use of synthetic chemical fungicides has led to M. oryzae becoming resistant (Khan et al., 2022). Second, *M. oryzae* possesses remarkable genomic plasticity and a high rate of evolution, allowing it to adapt rapidly to pressure from both chemical control agents and plant resistance genes (Al Mamun Khan et al., 2023; Li et al., 2025). Furthermore, the continued use of synthetic chemicals poses environmental hazards, leaves harmful residues in crops, and threatens human health and non-target organisms (Xun et al., 2023).

Plants produce a variety of specialized metabolites as a primary defense mechanism against microbial pathogens (Ramaroson et al., 2022). Phenylpropanoids, derived from the aromatic amino acid phenylalanine, encompass several bioactive classes, including flavonoids, phenolic acids, stilbenes, and coumarins, which mediate plant resistance through physical and chemical strategies (Kumari et al., 2023; Ortiz & Sansinenea, 2023; Ramaroson et al., 2022). Their antifungal relevance is characterized by several modes of action: (1) physical reinforcement, where phenylpropanoid derivatives facilitate cell wall lignification to create a mechanical barrier against fungal penetration (Devanna et al., 2022; Ortiz & Sansinenea, 2023); (2) membrane disruption, through changes in membrane permeability and integrity, leading to leakage of essential intracellular substances (Khan et al., 2022; Ramaroson et al., 2022; Xun et al., 2023); and (3) metabolic disruption, by targeting essential fungal enzymes. Specifically, these compounds can inhibit Succinate Dehydrogenase (SDH), thereby disrupting mitochondrial respiration and energy production (Cai et al., 2026; Khan et al., 2022), or block the glyoxylate cycle by inhibiting Isocitrate Lyase (ICL1), which is crucial for the development of infection structures such as the appressorium (Khan et al., 2022; Park et al., 2016). Furthermore, phenylpropanoid derivatives can neutralize secreted effectors such as MoErs1, effectively preventing the pathogen from suppressing host immunity and limiting its invasive capacity (Liu et al., 2024).

Molecular docking is an in silico method that can predict molecular binding and enable rapid screening of compounds with antifungal potential (Azad, 2023). In relation to blast disease, molecular docking was used to screen for ligands derived from the phenylpropanoid pathway that could bind to target proteins in *M. oryzae*. The results of molecular docking depend on the binding energies, number of hydrogen bonds, and potential hits found in the protein-ligand complex structure (Singh et al., 2022).

Despite the availability of various chemical fungicides, Magnaporthe oryzae rapidly develops resistance, primarily because most commercial agents target only one metabolic enzyme, which can be overcome by a single point mutation (Al Mamun Khan et al., 2023; Khan et al., 2022). While natural secondary metabolites of the phenylpropanoid pathway

are known for their bioactivity, there is a significant research gap regarding their specific molecular interactions and multi-site inhibitory potential against important M. oryzae targets (Al Mamun Khan et al., 2023; Khan et al., 2022). Most existing studies have focused on screening general antifungals without clarifying the structural basis for how these compounds interfere with fungal pathogenicity. The uniqueness of this study lies in the integrated in silico evaluation of phenylpropanoid derivatives against two distinct, high-value targets: the metabolic enzyme Isocitrate Lyase (ICL1), which is essential for energy assimilation during appressorium-mediated penetration, and the species-specific secretory effector MoErs1, which represents a breakthrough in fungicide design by targeting the fungus' ability to suppress host immunity (Khan et al., 2022; Liu et al., 2024). By identifying candidates that effectively bind both metabolic and virulence-related proteins, this study aims to provide a structural basis for developing biofungicides with multiple mechanisms of action, thereby reducing the likelihood of resistance emergence. This study aimed to identify potential phenylpropanoid-based antifungal compounds targeting Isocitrate Lyase (ICL1) and MoErs1 proteins of M. oryzae through an in silico approach.

2. Methods

This research was conducted from October 2025 to March 2026. Ligands Phenylpropanoid pathway were identified by reviewing literature and determining whether the ligands were flavonoids or their derivatives.

2.1 Selection and Preparation of Target Protein

The three-dimensional structure of the target protein associated with the pathogenicity of *Magnaporthe oryza*e was obtained from the Protein Data Bank. The proteins targeted in this study were: isocitrate lyases ICL1 (Protein Data Bank ID: 5e9f) with a resolution of 2.80 Å and secreted fungal effector protein MoErs1 (7vs2) with a resolution of 2.50 Å. Proteins were prepared by removing water molecules and co-crystallized ligands that may interfere with the docking simulations, adding polar hydrogen atoms to the protein structure to ensure proper hydrogen bonding interactions during docking, and assigning partial charges to the protein using the Kollman charge model. Protein preparations were performed using AutoDock Tools 1.5.7, and the proteins were converted to the pdbqt extension for molecular docking.

2.2 Ligand Selection and Preparation

A total of 317 phenylpropanoid-derived ligands were selected as candidate antifungal compounds in this study. The selection was performed based on the following criteria: (i) compounds classified within the phenylpropanoid group, including flavonoids, phenolic acids, coumarins, and related derivatives; (ii) availability of experimentally reported antimicrobial or antifungal activity in the literature; (iii) structural diversity to represent a broad range of chemical scaffolds within the phenylpropanoid class; and (iv) availability of complete three-dimensional structures in the PubChem database. Two reference ligands were employed for comparative analysis: tricyclazole (PubChem ID: 39040), a standard melanin biosynthesis inhibitor, and edifenphos (PubChem ID: 28292), an organophosphorus fungicide known for disrupting membrane integrity (Khan et al., 2022; Liu et al., 2024). The three-dimensional structures were retrieved from the PubChem database in SDF format, subsequently converted to PDB, and subjected to energy minimization using the Universal Force Field (UFF) to achieve stable low-energy

conformations. Preparation included the addition of polar hydrogen atoms and the assignment of Gasteiger partial charges via AutoDock Tools to ensure compatibility with the docking algorithms (Cai et al., 2026). The prepared ligand structures were then converted into PDBQT format using Open Babel and AutoDock Tools to ensure compatibility with the docking software.

2.3 Molecular Docking Simulation

The search space for molecular docking was defined by a grid box centered on the identified active site or interaction interface of each target protein. For Isocitrate Lyase (ICL1, PDB ID: 5E9F), the grid box was centered following the CASTP result (Binkowski et al., 2003) which was centered at x = -1.6421, y = 34.3112, and z = 31.0196 to encompass all critical residues in the binding pocket. While for the secreted effector MoErs1 (PDB ID: 7VS2), the grid box was strategically positioned to cover the L2 and B11 regions which have a more prominent role in the virulence of *M. oryzae* and centered at x = 26.301, y = 49.601, and z = 29.106 (Liu et al., 2024). Molecular docking simulations were performed using AutoDock Vina. The docking parameters were set with an exhaustiveness value of 8 and the number of output binding modes set to 9 for each ligand. During docking, the protein structures were treated as rigid, while ligand flexibility was allowed through rotatable bonds. Each ligand was docked into the defined binding site, generating multiple binding conformations. For each ligand, the conformation with the lowest binding energy was selected as the most stable complex. The binding affinity values were expressed in kilocalories per mole (kcal/mol), with the more negative values indicating stronger predicted binding interactions.

2.4 Analysis of Protein–Ligand Interactions

The docking results were analyzed to identify the binding poses and interaction patterns between the phenylpropanoid compounds and the target protein. Key interactions such as hydrogen bonding and hydrophobic interactions were examined to understand the molecular basis of ligand binding. To determine the bonds between the ligand and protein, the docking results were visualized in 2D using LigPlot+ and then validated by uploading the docking results to the Protein-Ligand Interaction Profiler on the website (https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index) (Schake et al., 2025).

3. Results and Discussion

To identify new antifungal candidates with high specificity, molecular docking simulations were performed on two key target proteins of *M. oryzae*. Simulations were performed three times to ensure internal reliability, with results presented as mean ± standard deviation (SD).

From the docking results with Isocitrate Lyase (ICL1, PDB ID: 5e9f), the majority of the ligands were in the range of -2.47 to -11.57 kcal/mol. The average docking results were then ranked from strongest to weakest binding affinity. Ten ligands with the strongest binding affinities are shown in Table 1, exhibited values ranging from -9.83 to -11.57 kcal/mol. Quantitatively, the best ligands such as Vitisin A (-11.57 kcal/mol) have significantly stronger binding stability, almost twofold, than the commercial references Edifenphos (-5.57 kcal/mol) and Tricyclazole (-6.13 kcal/mol). The low standard deviation values for the majority of ligands (0.06–0.81) indicate a high level of internal precision, proving that the stochastic search algorithm successfully achieved convergence

on consistent binding conformations in each iteration. Meanwhile, the SD value reaching 1.54 for Suffruticosol A indicates a greater variation in binding poses, which is likely due to the complex energy landscape or a larger number of rotable bonds, thus requiring a wider search of the conformational space to achieve optimal stability.

Table 1. Binding affinity of top ten ligands against Isocitrate Lyase (ICL1, PDB ID: 5e9f)

Ligand	PubChem CID	Binding Affinity (kcal/mol)	Standard Deviation
Edifenphos (Reference 1)	28292	-5.57	0.06
Tricyclazole (Reference 2)	39040	-6.13	0.23
Ellagitannin	10033935	-11.57	0.81
Vitisin A	16131430	-11.20	0.70
Vitisin C	16145527	-11.20	0.17
Suffruticosol A	10604579	-11.03	1.54
Sanggenon D	9987332	-10.57	0.42
Viniferol D	182979	-10.37	0.15
Gallotanin	16129878	-10.30	0.17
Miyabenol A	16129868	-10.13	0.71
Suffruticosol B	10652146	-10.07	0.23
Isohopeaphenol	21669382	-9.83	0.49

The lower the binding affinity value of a ligand to a protein, the less energy is required to bind and form a much more stable complex during the interaction (Al Mamun Khan et al., 2023; Cai et al., 2026). Ligand binding to a protein can cause the protein to not function properly. Isocitrate Lyase (ICL1) is one of the main enzymes in the glyoxylate cycle (Khan et al., 2022; Park et al., 2016). Theoretically, ICL1 is a key enzyme in the glyoxylate cycle that allows pathogens to assimilate two-carbon compounds into intermediates for energy metabolism and gluconeogenesis, especially under conditions of glucose deficiency in host cells. ICL1 catalyzes the first step in the glyoxylate cycle, which is the breakdown of isocitrate into succinate and glyoxylate. This glyoxylate cycle allows pathogens to assimilate two-carbon compounds into intermediates used for energy metabolism and gluconeogenesis, especially in glucose-deficient conditions (Park et al., 2016). A significant reduction in virulence was observed in fungi lacking ICL1 gene function (Khan et al., 2022), making ICL1 a primary target in the search for novel antifungals. In one study, the natural compound GKK1032A2 showed an affinity of -9.1 kcal/mol for ICL1, which was stronger than that of the reference ligand Strobilurin (-7.8 kcal/mol), making it a recommended fungicide base (Khan et al., 2022). Meanwhile, docking results in this study showed that the 10 ligands with the highest binding affinity had stronger binding than the reference ligand used in commercial antifungals. This indicated that these ten ligands have potential as novel antifungals against *M. oryzae.*

From the docking result targeted the Effector 1 Regulated by MoSyn8 (MoErs1, PDB ID: 7vs2), the majority of the ligands were in the range of -3.87 to -10.6 kcal/mol. The average docking results were then ranked from strongest to weakest binding affinity. The

ten ligands with the strongest binding affinities are shown in Table 2, exhibited values ranging from -9.17 to -10.60 kcal/mol. The low standard deviation observed (0.00–0.75) indicates high internal reliability and precision, confirming that the stochastic search algorithm consistently converged toward the most stable binding conformations across all replicates (Azad, 2023).

Table 2. Binding affinity of top ten ligands against Effector 1 Regulated by MoSyn8 (MoErs1, PDB ID: 7vs2)

Ligand	PubChem CID	Binding Affinity (kcal/mol)	Standard Deviation
Edifenphos (Reference 1)	28292	-5.23	0.06
Tricyclazole (Reference 2)	39040	-4.93	0.06
Ellagitannin	10033935	-10.60	0.00
Miyabenol A	16129868	-9.90	0.00
Vitisin A	16131430	-9.90	0.00
Viniferol D	182979	-9.80	0.00
Suffruticosol A	10604579	-9.80	0.00
Suffruticosol B	10652146	-9.80	0.00
Isohopeaphenol	21669382	-9.27	0.06
Hopeaphenol	44334030	-9.27	0.06
Sanggenon D	9987332	-9.20	0.00
Thearubigin	76182283	-9.17	0.75

Table 3. Binding affinity of the selected ligands against target proteins

Ligand	PubChem CID	Binding Affinity (kcal/mol)	
		ICL1 (PDB ID: 5e9f)	MoErs1 (PDB ID: 7vs2)
Edifenphos (Reference 1)	28292	-5.57	-5.23
Tricyclazole (Reference 2)	39040	-6.13	-4.93
Vitisin A	16131430	-11.57	-9.90
Miyabenol A	16129868	-10.13	-9.90
Viniferol D	182979	-10.37	-9.80
Suffruticosol A	10604579	-11.03	-9.80
Suffruticosol B	10652146	-10.07	-9.80
Isohopeaphenol	21669382	-9.83	-9.27

MoErs1 (Effector 1 Regulated by MoSyn8) is a cytoplasmic effector protein secreted by M. oryzae into host cells during infection (Liu et al., 2024). Its primary function is as a protease inhibitor that specifically targets the rice plant's papain-like cysteine protease, OsRD21 (Liu et al., 2024). MoErs1 will suppress the function of OsRD21, which plays an

important role in rice plant immunity. MoErs1 is a protein specific to M. oryzae and has no homologs in other species, making it an ideal target for new fungicides, and the risk of negative impacts on non-target organisms is very low. Ligands with stronger binding affinity are often correlated with better disease control capabilities in the field (Liu et al., 2024). In a study, compound FY21001, with its very low binding energy (-15.9 kcal/mol), was shown to significantly reduce crop losses due to blast (Liu et al., 2024).

The 10 ligands with the strongest binding affinities, six ligands had the strongest binding affinity in both dockings, and no direct reports demonstrated antifungal activity against Magnaporthe oryzae. These ligands are Vitisin A, Miyabenol A, Viniferol D, Suffruticosol A, Suffruticosol B, and Isohopeaphenol. A summary of the affinity values of these seven ligands can be seen in Table 3.

Then the types of interactions observed in ligand-protein binding and the amino acid residues involved were analyzed. This was important because it could predict the binding stability, inhibition mechanisms, and substrate specificity. Table 4 and Table 5 list the types of interactions found and the residues involved.

Table 4. Interaction of selected ligand with ICL1 protein

Ligand	Hydrophobic Interactions	Hydrogen Bonds	Other
Vitisin A	Lys28, Trp31, Arg41, Ala45	Lys28, Trp31, Ser32, Asp33, Arg41, Ala45, Glu46	π-Stacking (Trp31)
Miyabenol A	Trp31, Trp36	Trp36, Thr39, Arg41	π-Stacking (Lys28)
Viniferol D	Leu434, Pro436, **Trp440**, Ile453, Ile466, His472	Leu434, Arg446, **Gln449**	-
Suffruticosol A	Arg268, Ala271, Lys346, Asn390, Ile393	Arg268, Asp318, Lys346	-
Suffruticosol B	Leu434, Pro436, Ile453, Ile466, His472	**Trp440**, Leu468	π-Stacking (Trp440)
Isohopeaphenol	Trp31, Ala45	Lys28, Trp31, Thr39, Arg41, Phe43, Ala45, Glu46	π-Stacking (Trp31), π-Cation Interactions (Lys28)

Note: The residues in bold are residues located in the active site of the target protein.

From Table 4 and Table 5, it could be seen that the six selected ligands have Hydrophobic Interactions and Hydrogen Bonds, as well as π-Stacking in some ligands. In ligand-protein binding, Hydrophobic Interactions, Hydrogen Bonds, and π-Stacking interactions are the main non-covalent forces that determine the stability, affinity, and biological specificity of the formed complex. Hydrogen bonds contribute significant free energy to maintain the stability of the protein-ligand complex during the interaction and this interaction also shows the protein preference for binding to the substrate (Cai et al., 2026; S. Wang et al., 2019). In addition to hydrogen bonds, there are also Hydrophobic Interactions. Hydrophobic Interactions play an important role in defining the binding environment and ensuring the ligand can reach its target, namely by forming a binding pocket and clamping the substrate (Cai et al., 2026; S. Wang et al., 2019). Meanwhile, π-

stacking can significantly increase protein binding affinity, which correlates with stronger biological activity and forms electronic complementarity, enabling more stable binding with electron-deficient residues (Cai et al., 2026; S. Wang et al., 2019). The presence of these interactions indicates a strong ligand-protein bond.

Table 5. Interaction of selected ligand with MoErs1 protein

Ligand	Hydrophobic Interactions	Hydrogen Bonds	Other
Vitisin A	Arg28, Pro31, **Pro71, Phe72**	**Ser64**, Thr65, Arg212	-
Miyabenol A	Leu25, Arg28, Pro68, **Pro71**	Thr65, Val69, Arg212	-
Viniferol D	Phe155, Ala156, Thr159	Gln32, Ala156, Asn157, Thr159	π-Stacking (Phe155)
Suffruticosol A	Phe155, Thr159	Gln32, Ala156, Asn157, Thr159	π-Stacking (Phe155)
Suffruticosol B	Phe155, Thr159	Ala156, Asn157, Thr159	π-Stacking (Phe155)
Isohopeaphenol	Leu25, Arg28, **Pro71**	Ser64, Thr65, Glu66, Glu67, Ala70	-

Note: The residues in bold are residues located in the active site of the target protein.

Upon binding to MoErs1, the active site of the protein is located in the L2 and β11 regions, which play a more prominent role in the virulence of M. oryzae. The L2 residues are Ser64, Glu67, Pro71, Phe72, while the β11 residues are Arg178 and Asp180 (Liu et al., 2024) . We can see in Table 5 that Vitisin A, Miyabenol A, and Isohopeaphenol, ligands bind to residues located in L2 and/or β11. Meanwhile, for ICL1, the TRP440 and Gln 449 residues are crucial because these residues are in the active site that regulates fungal energy metabolism (Khan et al., 2022). The ligands Viniferol D and Suffruticosol B were observed to be bound to these residues. If the active site of an enzyme is blocked by a ligand, its functional activity will cease because the ligand prevents the natural substrate from entering and binding to the active site, so that biochemical reactions necessary for microbial survival or pathogenicity cannot occur (Al Mamun Khan et al., 2023; Khan et al., 2022). This further supported the antifungal potential of these ligands against *M. oryzae*.

All of these results indicated that several ligands have promising antifungal potential against *M. oryzae*. This potential was characterized by a stronger binding affinity than the commercial references, the presence of hydrophobic interactions and hydrogen bonds, and ligand binding to the protein's active site. Practically, these findings offer the opportunity to develop environmentally friendly phenylpropanoid-based biofungicides that could reduce dependence on hazardous synthetic chemicals. This is particularly relevant given the increasing resistance of M. oryzae to conventional fungicides.

However, this study has explicit limitations because it was entirely in silico-based using a rigid-receptor model, which may not fully capture the dynamic conformational changes of the protein. Furthermore, the simulations did not include explicit water molecules that could affect the binding free energy. Hence, further validation is still needed. Validation can be performed in silico using Molecular Dynamics (MD) Simulation, which can evaluate the stability of protein-ligand complexes under dynamic physiological conditions over a certain period of time (Al Mamun Khan et al., 2023; Khan et al., 2022; Singh et al.,

2022). Another in silico validation method is calculating the Bioactivity Score to predict the probability that a compound will function as an enzyme inhibitor or receptor ligand in biological assays (Al Mamun Khan et al., 2023; Khan et al., 2022). Further validation such as biochemical validation with Enzyme Inhibitory Assay (IC50) and biological validation with In Vitro Test (EC50) can be carried out to determine the concentration of compounds required to inhibit 50% of the target protein activity and measure the efficacy of the compounds in inhibiting the growth of fungal mycelia respectively (Cai et al., 2026; Xun et al., 2023).

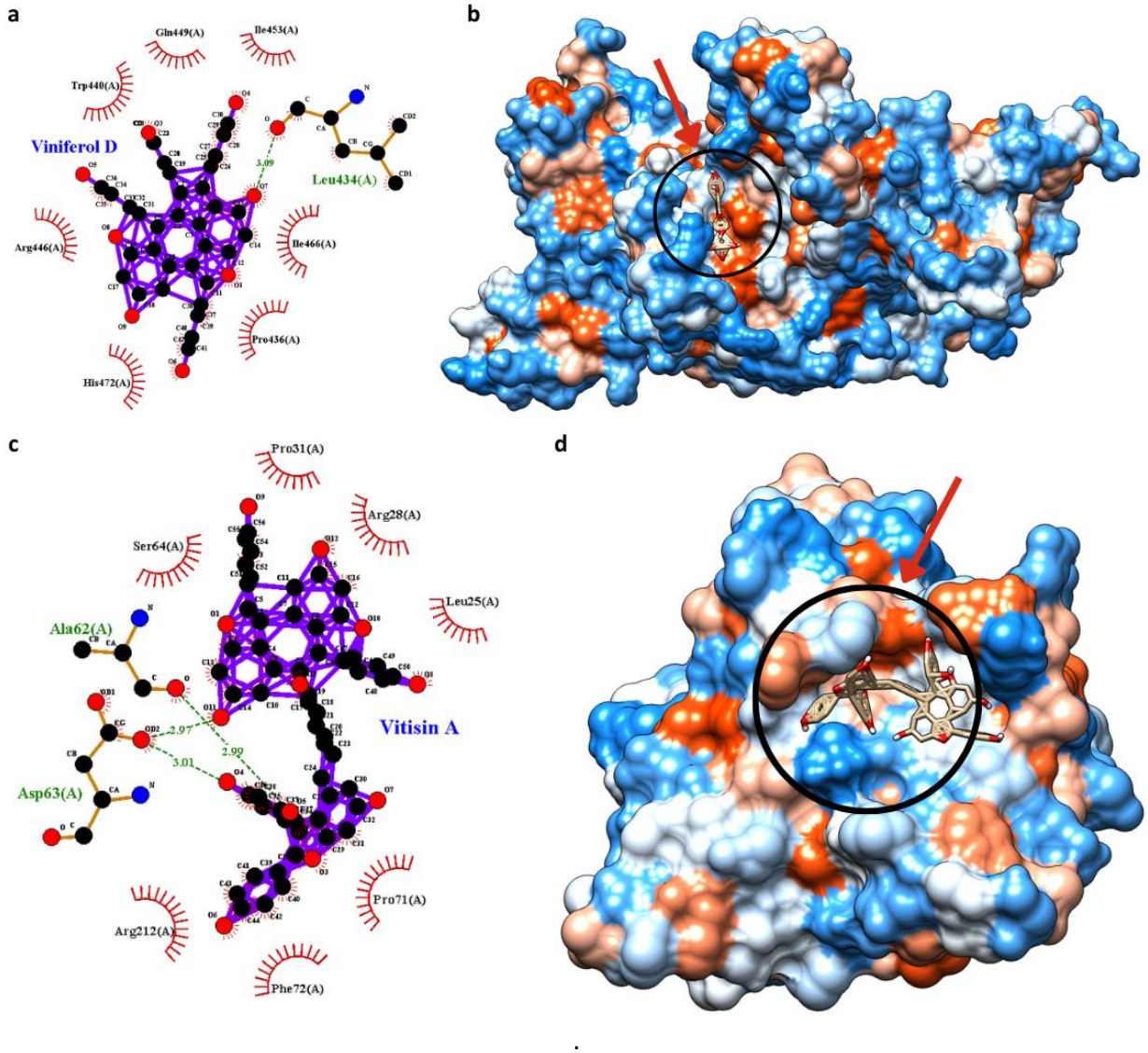

Figure 1. Two-dimensional (a, c) and three-dimensional (b,d) visualization of the interaction between ligand Viniferol D - ICL1 (a, b), and Vitisin D - MoErs1 (c, d) of the *M. oryzae*. Arrow and circle show where the ligand is bound to the protein.

4. Limitations and Future Directions

This study is subject to several inherent limitations associated with its exclusively in silico approach. The molecular docking simulations employed a rigid receptor model, which does not fully capture the dynamic conformational flexibility of proteins during ligand

binding under physiological conditions. Additionally, the absence of explicit solvent molecules and the reliance on simplified scoring functions may lead to inaccuracies in binding energy estimation and potential false-positive predictions. While the docking results demonstrate strong binding affinity and favorable interaction profiles, these findings remain predictive and do not directly confirm biological activity, antifungal efficacy, or toxicity in real biological systems.

Future research should prioritize multi-level validation to strengthen the reliability and applicability of these findings. Advanced computational methods such as Molecular Dynamics (MD) simulations are recommended to evaluate the stability and behavior of protein–ligand complexes over time. Furthermore, experimental validation through enzyme inhibition assays (IC_{50}), in vitro antifungal assays (EC_{50}), and in planta studies is essential to confirm efficacy under realistic conditions. Integrating pharmacokinetic and toxicity profiling, including ADMET analysis, will also be crucial for assessing the safety and practical feasibility of these compounds. Such a comprehensive approach will accelerate the development of phenylpropanoid-based biofungicides as sustainable alternatives for controlling rice blast disease.

5. Conclusion

This study successfully identified several phenylpropanoid-derived compounds, specifically Vitisin A, Miyabenol A, Viniferol D, Suffruticosol A, Suffruticosol B, and Isohopeaphenol, as highly promising antifungal candidates against Magnaporthe oryzae. Using a structure-based virtual screening approach, we achieved the primary objective of characterizing the molecular interactions and binding affinities of these natural products to important fungal targets. The identified ligands exhibited significantly stronger binding energies compared to commercial references such as Edifenphos and Tricyclazole, indicating superior complex stability and a higher probability of spontaneous binding. Detailed interaction analysis confirmed that these compounds effectively occupy the key active site domain, forming a network of multiple hydrogen bonds and hydrophobic interactions (including π−π stacking) with key residues. These findings provide a strong structural basis for the potential of these phenylpropanoids as key molecules that can disrupt the function of vital proteins and pathogenicity factors in the fungus that causes rice blast disease.

However, reliance on computational simulations introduces specific limitations that must be addressed to ensure the reliability of these findings. Current molecular docking protocols often utilize rigid receptor models, which fail to capture the dynamic "adjustment-induced" conformational changes or structural rearrangements that occur during actual ligand-protein recognition. Furthermore, the exclusion of explicit water molecules in the binding pocket and the use of simplified scoring functions can lead to overestimation of binding scores or false-positive identifications. To address these constraints, future research should prioritize Molecular Dynamics (MD) simulations to evaluate the temporal stability and flexibility of the complex under physiological conditions. Further experimental validation through in vitro antifungal assays (determining EC50/IC50 values), enzyme inhibition studies, and in planta field trials are mandatory to confirm the biological efficacy and environmental safety of these candidates. This integrated workflow will build a strong foundation for developing these phenylpropanoids as environmentally friendly biofungicides for sustainable rice blast disease management.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

In the preparation of this article, the authors did not use artificial intelligence (AI) assistance.

Authors' Contributions

Fidelia Sihombing: conceived the study design, conducted research, collected data, analyzed, wrote, reviewed, and edited.

Declaration of Competing Interests

The authors stated that they had no interest that might be perceived as posing a conflict or bias.

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