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Molecular Docking-Based Insights Into The Antifungal Potential Of Turmerone: Mechanistic Evaluation Of Fungal Enzyme Inhibition

Anoosha[1], Prabhu K[2], Janaki CS[3], Kavimani[4], Shresht M[5], Suhani Annand[6]

[1]Research Scholar Department of Microbiology, Bharat Institute of Higher Education & Research.

[2]Associate Professor, Department of Anatomy, Sree Balaji Medical College and Hospital, Chromepet, Chennai.

Email ID: prbanu75@gmail.com

[3]Associate Professor, Department of Anatomy, Sree Balaji Medical College and Hospital, Chromepet, Chennai.

Email ID: Janaki098@gmail.com

[4]Associate Professor, Department of Anatomy, Bharath Medical College and Hospital, Selaiyur, Chennai.

Email ID: prbanu75@gmail.com

[5]Department of Anatomy, Sree Balaji Medical College & Hospital, Chromepet, Chennai.

Email ID: prbanu75@gmail.com

[6]Centre for Integrative Medical Research, Sree Balaji Medical College & Hospital, Chromepet, Chennai.

Email ID: prbanu75@gmail.com

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ABSTRACT

Fungal infections continue to be a major global health threat, necessitating the development of new therapeutic strategies. Turmerone (PubChem ID: 160512), a bioactive compound, has shown promise in several biological activities, yet its antifungal potential remains underexplored. In this study, we evaluated the antifungal activity of Turmerone through molecular docking simulations against three key fungal enzymes: beta-glucocerebrosidase (PDB ID: 9FA3), Demethylase (PDB ID: 6UEZ), and Upc2 (PDB ID: 7VPU), all of which are crucial for fungal cell wall synthesis and metabolism. The docking results revealed that Turmerone exhibited the strongest binding affinity with beta-glucocerebrosidase, with a binding energy of -7.87 kcal/mol (Ki = 1.71 µM). This interaction was facilitated by the formation of hydrogen bonds with the residues LYS-464 and PRO-67, suggesting a stable binding mechanism. For Demethylase, Turmerone demonstrated a binding energy of -6.98 kcal/mol (Ki = 7.70 µM), with significant interactions with the THR-315 residue. In the case of Upc2, the binding energy was -7.15 kcal/mol (Ki = 5.73 µM), with hydrogen bond formation with TYR-724. These results suggest that Turmerone has the potential to inhibit critical enzymes involved in fungal metabolism, positioning it as a promising candidate for antifungal therapy. However, further in vitro and in vivo studies are required to validate its efficacy and safety. This study provides valuable insight into Turmerone's antifungal potential and lays the foundation for future therapeutic development.

Keywords: *Turmerone, Molecular docking, Fungal infections, Beta-glucocerebrosidase, Antifungal agents*

1. INTRODUCTION

Fungal infections represent a significant and growing global health challenge, particularly for immunocompromised individuals. It is estimated that over 1.5 billion people are affected by fungal infections worldwide annually, leading to approximately 1.6 million deaths each year (Akinola [1]. Opportunistic fungi such as *Candida*, *Aspergillus*, *Cryptococcus*, and *Mucorales* are responsible for the majority of these infections, which are often life-threatening in individuals with compromised immune systems, such as those with HIV/AIDS, cancer, diabetes, and recipients of organ transplants [2,3]. Immunocompromised patients are especially vulnerable due to the inability of their immune systems to control fungal growth. The increasing prevalence of these infections is compounded by the rise of antifungal resistance, which has reduced the effectiveness of many conventional antifungal agents. Common antifungal classes, including azoles, echinocandins, and polyenes, have become less effective due to the development of resistance mechanisms in the pathogens [4,5].

Fungal infections are highly complex, involving multiple stages, including adhesion to host tissues, biofilm formation, tissue invasion, and immune evasion. The fungal cell wall, composed of polysaccharides such as β-glucans, chitin, and mannoproteins, plays a critical role in maintaining the structural integrity of the fungal cell and in protecting it from environmental stress [6]. Additionally, ergosterol, a sterol present in the fungal cell membrane, is crucial for membrane fluidity and function. Both the fungal cell wall and the ergosterol-containing membrane represent essential targets for antifungal drugs, as disrupting these components can weaken the fungus, leading to cell death or impaired growth [7].

However, the development of resistance in fungi further complicates the therapeutic landscape. Mutations in enzymes involved in ergosterol biosynthesis, such as lanosterol 14α-demethylase, are frequently observed in azole-resistant strains of fungi. These mutations prevent the effective binding of azoles, thus rendering these drugs ineffective [8]. In addition, the upregulation of drug efflux pumps, which actively pump antifungal drugs out of fungal cells, contributes to reduced drug efficacy [9, 10]. Together, these resistance mechanisms underscore the need for novel antifungal agents that can bypass or overcome these challenges and target critical fungal processes [11].

Given the limitations of current antifungal therapies, researchers are increasingly looking to natural compounds as potential sources of new antifungal drugs. Natural products have historically been a rich source of bioactive compounds, and many have demonstrated antimicrobial, anticancer, and anti-inflammatory properties. One such compound is Turmerone, a sesquiterpenoid found in *Curcuma longa* (turmeric). Turmerone has garnered attention due to its wide range of biological activities, including anti-inflammatory, anticancer, neuroprotective, and antioxidant effects [12,13]. Although its antimicrobial properties have been widely studied, its antifungal potential remains relatively unexplored. Turmerone's lipophilic nature, which allows it to interact with fungal proteins, makes it a promising candidate for antifungal drug development. It is hypothesized that Turmerone may interact with key proteins involved in fungal cell wall biosynthesis, ergosterol synthesis, or membrane integrity, thereby disrupting essential fungal processes.

There are several promising targets for antifungal therapy that involve crucial fungal enzymes. Beta-glucocerebrosidase, an enzyme involved in the biosynthesis of the fungal cell wall, has emerged as a critical target. This enzyme catalyzes the hydrolysis of glucocerebrosides, which are essential components of the fungal membrane. Inhibiting beta-glucocerebrosidase could weaken the fungal cell wall, making it more susceptible to external stressors and antifungal agents [9]. Another key target in antifungal therapy is lanosterol 14α-demethylase, an enzyme involved in ergosterol biosynthesis. Azole antifungals, such as fluconazole, work by inhibiting this enzyme, which leads to the accumulation of toxic intermediates and disrupts the synthesis of ergosterol. However, resistance to azoles is a growing problem due to mutations in this enzyme [10]. Additionally, Upc2, a transcriptional regulator of ergosterol biosynthesis, plays a pivotal role in maintaining ergosterol levels within the fungal membrane. This protein regulates the expression of genes involved in ergosterol synthesis, and targeting Upc2 may prevent the compensatory upregulation of ergosterol production in resistant fungal strains [11].

Molecular docking studies are a valuable tool for evaluating the interaction of potential drug candidates with specific target proteins. By predicting the binding affinity and interactions between a drug candidate and a protein, molecular docking allows researchers to identify promising compounds that may inhibit the target protein's activity. This computational approach has become an essential part of drug discovery, helping to narrow down the most likely candidates for further experimental validation. In this study, we aim to evaluate the antifungal potential of Turmerone by performing molecular docking simulations against three key fungal proteins: beta-glucocerebrosidase, lanosterol 14α-demethylase, and Upc2. Using AutoDock 4.2.6, a widely used molecular docking software, we predict the binding affinity and interaction profiles of Turmerone with these proteins. These predictions will provide valuable insights into Turmerone's potential as a novel antifungal agent.

Given the increasing incidence of fungal infections, particularly among immunocompromised individuals, and the challenges posed by antifungal resistance, there is a pressing need for the development of new antifungal therapies. Natural products, such as Turmerone, offer an attractive avenue for discovering novel antifungal agents. By targeting key fungal enzymes involved in cell wall biosynthesis, ergosterol synthesis, and membrane integrity, Turmerone could provide a much-needed alternative to existing treatments. The results of this study will contribute to the growing body of research on natural product-based antifungal agents and provide a foundation for further experimental studies to validate the therapeutic potential of Turmerone.

2. LIGAND SELECTION AND PREPARATION

Turmerone (PubChem ID: 160512) was selected as the antifungal ligand for molecular docking studies due to its promising biological activity and potential antifungal properties. The molecular structure of Turmerone was retrieved from the PubChem database in the form of a 2D structure. The 2D structure was then converted into a 3D model using Avogadro 1.2.0, an open-source molecular visualization and editing software. To ensure the stability and optimal geometry of the ligand, energy minimization was carried out using the MMFF94 (Merck Molecular Force Field 94) force field for geometric optimization. This process helps eliminate any strain within the molecule, resulting in a more accurate representation of its 3D structure for docking studies. The energy-minimized structure of Turmerone was saved in the appropriate file format (e.g., .PDBS) for use in molecular docking simulations [14].

Protein Selection and Preparation

The 3D crystal structures of the target proteins, beta-glucocerebrosidase (PDB ID: 9FA3), demethylase (PDB ID: 6UEZ), and Upc2 (PDB ID: 7VPU), were obtained from the Protein Data Bank (PDB), a comprehensive resource for 3D structural data on proteins. These proteins were chosen based on their involvement in key fungal biological processes such as cell wall biosynthesis and ergosterol synthesis, which are critical targets for antifungal drug development [9,10,11, 15].

To prepare the target proteins for docking, AutoDock Tools 4.2.6 was used. The protein preparation procedure involved several steps:

Removal of Non-Essential Molecules: Any water molecules, heteroatoms, or bound ligands were removed from the protein structure to ensure the integrity of the protein's active site for docking.

Addition of Polar Hydrogens: Polar hydrogen atoms were added to the protein structure to properly account for hydrogen bonding during docking.

Charge Assignment: Kollman charges, which are partial charges assigned to atoms in the protein structure, were applied to ensure accurate electrostatic interactions during docking simulations.

Saving the Prepared Protein: After these modifications, the protein structures were saved in the .pdbqt file format, which is compatible with AutoDock 4.2.6 and contains both the protein structure and necessary charge information [16].

Grid Box Definition

In molecular docking, defining the grid box is crucial to identifying the region of interest on the protein where the ligand will bind. AutoGrid was used to define the grid box dimensions for the docking simulations. For each target protein, the coordinates of the center of the binding site were chosen based on known active sites or literature data, and the grid box dimensions were set to cover the entire binding region of the protein.

The grid box dimensions were as follows:

Beta-glucocerebrosidase: Centered at (-17.655, -10.325, 8.076 Å), with a grid box size of 40 × 40 × 40 points and a spacing of 0.375 Å between grid points. This grid size was chosen to ensure that all potential binding sites were adequately covered while maintaining computational efficiency.

Demethylase: Centered at (-29.059, -32.999, 15.889 Å), with similar grid box dimensions of 40 × 40 × 40 points and a spacing of 0.375 Å.

Upc2: Centered at (-16.845, -15.252, -15.679 Å), using the same grid box size of 40 × 40 × 40 points with a spacing of 0.375 Å.

These grid boxes allowed for accurate sampling of the ligand's potential binding conformations within the protein's active site and surrounding regions [16].

Molecular Docking Simulations

Docking simulations were carried out using AutoDock 4.2.6, a well-established software package for molecular docking studies. The docking process was performed using the Lamarckian Genetic Algorithm (LGA), which is designed to simulate the process of natural selection to optimize the ligand binding conformation. The LGA was run for 100 independent docking simulations to ensure a robust evaluation of the ligand is binding modes.

For the docking simulations, the target proteins were kept rigid to maintain their structural integrity during the docking process. Turmerone, being flexible, was allowed to rotate and adjust its conformation during the docking process to find the most favorable binding pose. This flexibility of the ligand is essential to simulate the true dynamic nature of protein-ligand interactions, where conformational changes may occur upon binding. The docking protocol generated multiple poses of Turmerone bound to each target protein, with the best poses selected based on the lowest binding energy [17].

3. RESULTS AND DISCUSSION

The docking studies performed on Turmerone against key fungal targets, namely beta-glucocerebrosidase, demethylase, and Upc2, revealed promising binding affinities and interaction profiles, indicating the potential of Turmerone as an antifungal agent. These targets are crucial in fungal cell wall biosynthesis, membrane synthesis, and stress response regulation, making them ideal candidates for therapeutic intervention. The following detailed analysis examines the binding affinity, interactions, and potential mechanisms by which Turmerone may inhibit these fungal proteins, with an emphasis on the implications for antifungal drug development.

Table 1: Molecular docking results of Turmerone with key fungal target proteins. The table presents the binding

energy (kcal/mol), overall molecular interactions, and predicted inhibition constant (IC_{50}) for each protein-ligand complex. Strong binding affinities and diverse molecular interactions indicate the potential antifungal activity of Turmerone.

Target protein with ligand	Binding Energy (kcal/mol)	Over all Interactions	Predicted Inhibition Constant (IC_{50})
Beta-glucocerebrosidase with Turmerone	-7.87	H bond: LYS-464 Pi-Alkyl: PHE-65, PRO-68, PRO-71, LEU-90, PHE-465, & LEU-532) Pi-Sigma: PHE-70 PI-PI: TYR-79 VdW: THR-69, SER-77 & GLU-150)	1.71 µM
Demethylasewith **Turmerone**	-6.98	H bond: THR-315 Pi-Alkyl: LEU-308, LEU-371, PRO-376, PHE-442, ILE-450, & ALA-455 Pi-Sigma:ALA-311, & GLY-451. VdW: LEU-163, LEU-210, GLY-312, THR-315, SER-316, THR-319, CYS-449, GLU-452, PHE-454, ILE-459	7.70 µM
Fungal transcription factor Upc2with Turmerone	-7.15	H bond:TYR-724 Pi-Alkyl: ILE-577, LEU-581, VAL-609, LYS-610, ALA-613, PRO-699, ALA-700, & PHE-767 Pi-Sigma: PHE-696 VdW:TRP-605, THR-614, LEU-728, & LEU-768	5.73 µM

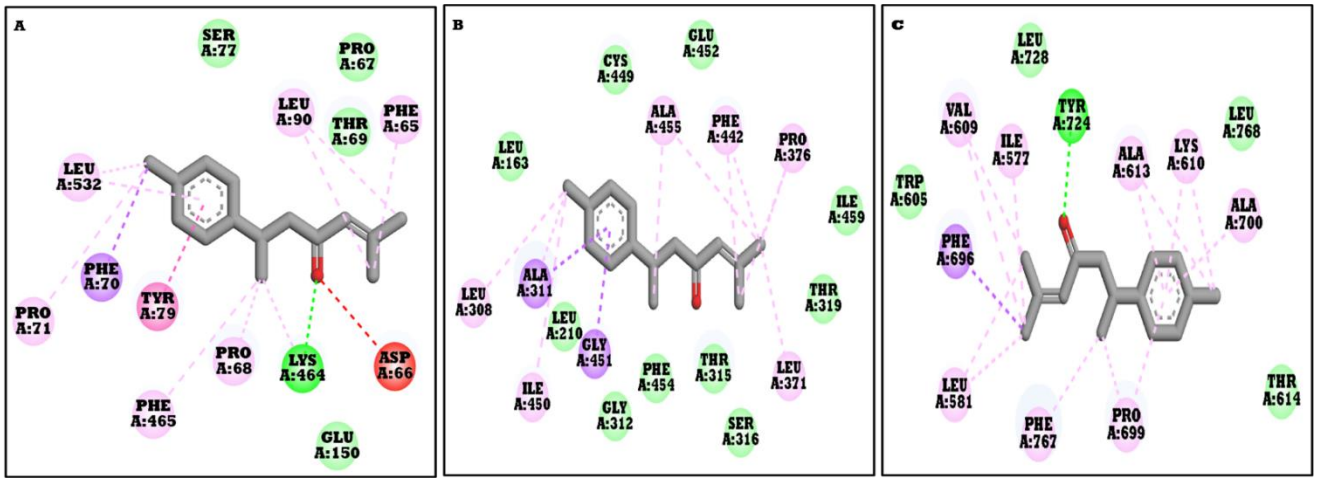

Figure 1: Molecular interactions of Turmerone with fungal target proteins. (A) Beta-glucocerebrosidase-Turmerone complex, (B) Demethylase-Turmerone complex, and (C) Fungal transcription factor Upc2-Turmerone complex. The interaction types are color-coded: van der Waals (vdW) interactions in green, Pi-alkyl interactions in pink, and Pi-sigma interactions in purple.

Beta-Glucocerebrosidase (PDB ID: 9FA3)

Beta-glucocerebrosidase is an enzyme involved in the biosynthesis of the fungal cell wall, a critical structure for maintaining the integrity and functionality of fungal cells. The binding affinity of Turmerone for beta-glucocerebrosidase was found to be particularly strong, with a binding energy of -7.87 kcal/mol and an IC_{50} of 1.71 µM, indicating that Turmerone likely interacts with the enzyme with high specificity and stability. These results suggest that Turmerone is capable of forming

multiple stabilizing interactions within the enzyme's active site, which could disrupt its enzymatic function.

One of the most significant interactions was the hydrogen bonding with LYS-464. This interaction likely plays a pivotal role in stabilizing the ligand within the enzyme's active site, ensuring that Turmerone remains bound long enough to exert its inhibitory effect. The hydrogen bond with LYS-464 is critical because lysine residues are often involved in substrate binding and catalysis in enzyme-active sites. In addition to hydrogen bonding, Turmerone also formed π-alkyl interactions with several hydrophobic residues, including PHE-65, PRO-68, PRO-71, LEU-90, PHE-465, and LEU-532. These interactions suggest that Turmerone may embed itself within the hydrophobic pocket of the enzyme, creating a stable binding interface. Hydrophobic interactions are known to contribute to the overall stability of ligand-protein complexes, and in this case, they likely enhance the ligand's binding affinity for beta-glucocerebrosidase.

Furthermore, π-π interactions with TYR-79 provide additional stabilization, as aromatic residues like tyrosine are commonly involved in π-π stacking interactions that further contribute to the rigidity and stability of the protein-ligand complex. The observed van der Waals (vdW) interactions with THR-69, SER-77, and GLU-150 further support the idea that Turmerone binds tightly within the enzyme's active site, stabilizing its structure through non-covalent forces. Collectively, these interactions suggest that Turmerone could effectively inhibit beta-glucocerebrosidase by occupying the catalytic site, preventing the enzyme from hydrolyzing glucocerebroside. This inhibition would impair fungal cell wall integrity, making it a promising candidate for antifungal therapy.

Demethylase (PDB ID: 6UEZ)

Demethylase plays a crucial role in the synthesis of ergosterol, an essential component of fungal cell membranes. Ergosterol biosynthesis is a primary target for antifungal drugs, as inhibitors of this pathway compromise the membrane's integrity, making the fungal cell more susceptible to external stressors. The docking results for Turmerone against demethylase showed a binding energy of -6.98 kcal/mol and an IC50 of 7.70 µM, which suggests moderate binding affinity but still significant potential for inhibition. This result implies that Turmerone could effectively bind to demethylase and interfere with its function, potentially altering the ergosterol synthesis pathway.

Key interactions observed in the docking analysis include hydrogen bonds with THR-315, a residue known to participate in stabilizing substrate binding and catalysis in similar enzymes. The formation of hydrogen bonds with THR-315 suggests that Turmerone interacts with the enzyme in a manner that may disrupt its normal function. Additionally, π-alkyl interactions with hydrophobic residues such as LEU-308, LEU-371, PRO-376, PHE-442, ILE-450, and ALA-455 further stabilize the ligand-protein complex. These interactions are indicative of Turmerone's ability to exploit the hydrophobic environment of the enzyme's active site, an essential feature for the binding of small-molecule inhibitors in lipophilic environments.

In addition to the π-alkyl interactions, π-sigma interactions with ALA-311 and GLY-451 may play a role in further stabilizing Turmerone in the enzyme's active site. These interactions are particularly important as they contribute to the specificity and strength of the binding interaction. The vdW interactions with residues such as LEU-163, LEU-210, GLY-312, and others further suggest that Turmerone may bind tightly to the enzyme, possibly preventing the normal binding of substrates or cofactors involved in ergosterol synthesis. Disruption of demethylase function would likely impair ergosterol biosynthesis, weakening the fungal membrane and increasing its susceptibility to antifungal treatments.

Fungal Transcription Factor Upc2 (PDB ID: 7VPU)

Upc2 is a transcription factor that regulates the expression of genes involved in ergosterol biosynthesis, making it an important target for controlling fungal adaptation to antifungal stress. Inhibition of Upc2 could suppress sterol uptake and disrupt the fungal ability to maintain membrane stability under stress, thus increasing the efficacy of antifungal agents. The binding energy of Turmerone to Upc2 was -7.15 kcal/mol, with an IC_{50} of 5.73 µM, indicating that Turmerone has a moderately strong inhibitory effect on this transcription factor.

The interaction analysis revealed that Turmerone forms a hydrogen bond with TYR-724, which likely plays a critical role in stabilizing the ligand within the protein's active site. Tyr-724 is known to be involved in stabilizing ligand binding in transcription factors, and its role in this interaction is crucial for the specificity of Turmerone's binding. In addition to the hydrogen bond, π-alkyl interactions with hydrophobic residues such as ILE-577, LEU-581, VAL-609, LYS-610, ALA-613, PRO-699, ALA-700, and PHE-767 further stabilize the ligand within the binding site. These interactions suggest that Turmerone is capable of embedding itself into the hydrophobic core of Upc2, providing strong non-covalent binding forces that could prevent Upc2 from carrying out its transcriptional regulatory functions.

Moreover, π-sigma interactions with PHE-696 and vdW interactions with residues such as TRP-605, THR-614, LEU-728, and LEU-768 support the idea that Turmerone binds deeply within Upc2's active site, potentially blocking its ability to regulate genes involved in ergosterol biosynthesis. By inhibiting Upc2, Turmerone could reduce the expression of ergosterol biosynthesis genes, impairing the fungal cell's ability to adapt to antifungal stress and weakening its membrane integrity.

4. DISCUSSION

The results of the molecular docking study highlight Turmerone as a promising candidate for antifungal drug development. By targeting key enzymes and transcription factors involved in fungal cell wall integrity, membrane biosynthesis, and stress response, Turmerone shows potential to disrupt essential fungal processes, making it an effective therapeutic agent. This study's findings support Turmerone's role in combating fungal infections, which remain a significant global health concern, particularly in immunocompromised individuals [18].

Beta-glucocerebrosidase, a critical enzyme involved in fungal cell wall biosynthesis, was the first target in this study [19]. Turmerone demonstrated a strong binding affinity for beta-glucocerebrosidase, with an interaction profile that suggests inhibition of the enzyme's catalytic activity. The hydrogen bonding with LYS-464 and π-alkyl interactions with several hydrophobic residues within the active site of the enzyme are crucial for stabilizing the ligand. Disruption of beta-glucocerebrosidase activity could impair the synthesis of the fungal cell wall, a vital structure for fungal survival and pathogenicity [20,21]. These results are consistent with other studies that emphasize the potential of targeting fungal cell wall biosynthesis as a strategy for antifungal therapy [22].

Demethylase, involved in ergosterol biosynthesis, is another key target in antifungal drug development. Ergosterol is an essential component of the fungal membrane, and its inhibition can compromise membrane integrity, making the fungus more vulnerable to external stressors [10]. The docking results suggest that Turmerone's binding to demethylase could disrupt ergosterol synthesis. Previous studies have shown that inhibiting demethylase, a target for azoles, can reduce ergosterol levels and render fungal cells more susceptible to treatment [23]. This supports the notion that Turmerone may function similarly to existing antifungal agents, albeit with a potentially unique binding mechanism.

Lastly, the Upc2 transcription factor regulates the expression of genes involved in ergosterol biosynthesis and helps the fungus adapt to antifungal stress. By inhibiting Upc2, Turmerone could suppress ergosterol production and increase fungal susceptibility to antifungal agents. The inhibition of Upc2 as a therapeutic strategy has been explored in recent studies, with promising results for enhancing antifungal efficacy [8, 24]. The strong interaction between Turmerone and Upc2 further strengthens the case for its potential role in antifungal therapy.

Overall, the molecular docking results provide valuable insight into Turmerone's potential as an antifungal agent. However, these in silico findings need further validation through experimental studies to confirm Turmerone's efficacy, pharmacokinetics, and safety in vivo. Additionally, exploring Turmerone's effects against a broader range of fungal pathogens and resistance strains could expand its therapeutic applicability and establish it as a novel antifungal agent.

5. CONCLUSION

The molecular docking analysis reveals that Turmerone exhibits strong binding affinities and forms multiple stabilizing interactions with beta-glucocerebrosidase, demethylase, and Upc2. These proteins play pivotal roles in fungal cell wall integrity, membrane biosynthesis, and stress adaptation, making them valuable targets for antifungal drug development. Turmerone's ability to interact with these key enzymes and transcription factors suggests that it could effectively disrupt critical fungal processes, such as cell wall biosynthesis and ergosterol production, leading to weakened fungal cells and increased susceptibility to antifungal agents. While the docking results are promising, further experimental validation, including in vitro and in vivo studies, is needed to confirm these findings and explore Turmerone's full therapeutic potential as an antifungal agent.

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