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Molecular Docking Approach to Identify Potential AntiCandidal Potential of Curcumin

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ABSTRACT

Background: Candida albicans is a kind of fungus that can lead to mortality. In the presence of the enzyme Lanosterol-demethylase, Ergosterol, the major sterol in the fungal cell membrane, is the resulting product of Lanosterol (Cytochrome P450DM).

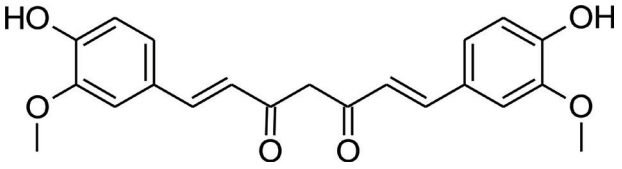
Purpose: Azole antifungal drugs target this enzyme as a target enzyme. The work included selecting and modelling the target enzyme. Cucumin's inhibitory effect on Cytochrome P450 was tested utilising molecular docking experiments.

Methods: Chem sketch was used to create compound structures, and Molergo Virtual Docker was used to do molecular docking.

Results: All of the curcumin and conventional medicines, such as Ketoconazole, Clotrimazole, and Miconazole, have interaction with 14-demethylase amino acid residues, Haem and water molecules in the target site, as per the docking research.

1. Introduction

Curcuma longa is a plant that belongs to Zingiberaceae family. Traditionally used in conjunction with traditional therapy for the cureof diverse illnesses, including gynaecological, gastrointestinal, hepatic impairment, infectious infections, and blood problems. It may be found in tropical Asia as well as certain African countries. Haldi is the traditional name for it in India. India is recognized as a major producer of *Curcuma longa*, and its export is highly valued in many other nations (Gargoubi et al. 2015). The plant's root is elongated, oval, and has a short branch. Curcumin is the main active component in Curcuma longa, accounting for 2 to 6% of the condiment (Eigner & Scholz, 1999; Govindarajan & Stahl, 1980). In 1815, Vogel and Pelletier discovered curcumin, a yellow colouring substance from *Curcuma longa* (Bandyopadhyay, 2014). Lampe and Milobedeska elucidated the configuration of a diferuloylmethane in 1910, and it was shown to occur in keto-enoltautomers (Prasad et al., 2014; Trujillo et al., 2013).



Antifungal drugs are widely used as agents that selectively remove fungal pathogens from a host with minimal toxicity to the host and are used to treat a variety of fungal infections (Hay, 2006). As a result of the extensive use of antifungal medicines, bacteria develop resistance to these treatments, increasing the risk of serious infections (Menozzi, 2004).

Resistance and severe side effects are some of the disadvantages of the medicines currently on the market for treating fungal infections. This has resulted in the search for novel antifungals that are both safe and effective (Gupta, Rani & Kumar, 2012; Rani, Sharma & Singh, 2015).

The 14-demethylase enzyme is involved in the ergosterol production, which leads to the development of cell walls. As a result, fungal cell wall production is inhibited, and therefore fungus development is inhibited (Arif et al., 2009; Fromtling, 1988).

Computational methods are an important part of the drug development process, from lead identification through lead optimization. One of the most commonly utilized techniques for hit identification is molecular modelling (Kitchen et al., 2004). It's method which is based upon energy scores that determines the most vigorously valuable molecule pose in the target binding. The general notion is that the lower the scores, the better is the enzyme-

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molecule binding. As a result, the study may be utilized as an optimization tool to discover the molecule-binding with the lowest energy Thomsen & Christensen, 2006). In continuation of our work on antifungals (Rani, Sharma, Gupta & Singh, 2013; Rani, Sharma & Singh, 2013; Rani & Singh, 2018; Rani, Kumar, Singh & Sharma, 2015; Rani & Singh, 2017; Rani, Kumar & Singh, 2019; Rani & Singh, 2019; Rani & Singh, 2019a; Rani, Kumar & Singh, 2020) and the need for the development of natural compounds with the ability to eliminate fungal diseases.

2. Materials and Methods

2.1. Enzyme Preparation

The anti-Candida potential of the examined molecules was assessed using *Candida albicans* demethylase enzyme. Furthermore, because the crystallographic structure of *Mycobacterium tuberculosis* demethylase and Candida albicans is structurally similar, the crystallographic structure of *M. tuberculosis* demethylase was chosen for the evaluation with Protein Data Bank ID 1EA1 (Varoli, Burnelli, Garuti & Vitali, 2001).

2.2. Molecule Preparation

Chem Sketch was used to create model structures of curcumin and reference chemicals such as ketoconazole, miconazole, and clotrimazole. These structures were converted to software's preferred format i.e. Mol (2000) files.

2.2.1. Target Site Prediction

The target site prediction in CYP450 was done using MVD software, and five sites were predicted. In addition, the site with the greatest volume, 189.4, and having the hem molecule was chosen. The presence of fluconazole at the same location predicted the confirmation of the site.

2.2.2. Enzyme Selection

The crystallographic moleculei.e. Fluconazole, Hem molecule, water molecules, and under studymolecule were all imported into Molergo Virtual Docker (MVD 2010.4.1.0) for docking. The target site of the enzyme was discovered, and the area that involves interaction with the imported molecule was chosen as the optimal docking region. The bioactive molecule was identified as the shape with the lowest energy (Rani & Singh, 2019; Rani & Singh, 2019a; Rani, Kumar & Singh, 2020).

2.2.3. Docking and Binding Evaluation

The molecules were examined for docking in the target site of demethylase of the under test fungal strain utilising MVD work systems. The docking was done in a stiff enzyme target site with a flexible molecule. The docking procedure begins with the insertion of a low-energy target molecule. Chem Draw programme was used to create the molecular structures, which were then saved as Mol files. These molecules were loaded into the programme, and the software automatically reduced their energy.

The target site, with a volume of 189.4 cubic metres and a surface area of 444.1 square metres and a grid size of fifteen radius, was chosen. Grid size resolution of 0.30 was used to improve a variety of beginning settings. Molecules were evaluated for docking in the target site, and the confirmation with the least score was chosen as the most potentpose.

The results were expressed in kcal/mol as a docking score. The H-bonding of the docked molecule with the enzyme residues of the target site was used to interpret the docked molecule–P450 demethylase CPY51 complex. Other compounds were docked in the target site of demethylase CPY51 enzymes using the same technique.

2.2.4. Docking Protocol Validation

The authenticity of the docking data was confirmed by comparing the docked posture of the co-crystallized molecule to its bound pose. The results depicted that the fluconazole was present in the same position as previously existing molecule. The RMSD for enzyme-molecule-standard was also found to be zero, indicating that the docking procedure may be trusted to predict binding mode.

3. Results and Discussion

To explore the anti-Candidal property of the substances, the chimeric enzyme was chosen, modelled, and energy was reduced. Molergo Virtual Docker was used to analyse this energy-minimized model for molecular modelling. It's a novel interrogative search method that depends on "guided differential evolution", which blends cavity prediction with the differential evolution optimization approach. The entire benchmarking procedure is entirely automated because to this automatic cavity prediction, enzyme and molecule preparation (Rani & Singh, 2019; Rani & Singh, 2019a; Rani, Kumar & Singh, 2020).

The chimeric protein, together with the molecules, Hemmolecule, and water molecules, was imported into the 14-α-demethylase enzyme for molecular modelling. For molecule binding, the optimal area comprising imported molecule and closer to the Hemmolecule was chosen. After that, energy reduction was achieved using MVD with ten separate docking experiments for each molecule.

Curcumin interacts with enzyme residues, and roughly three amino acid residues, Thr 260, Ser 252, and His 78,

are required for molecule binding, according to molecular modelling studies. The enzyme-molecule interaction represents the molecule's binding affinity for the enzyme (Maurice, Tuarira & Mwambete, 2009).

Table 1: Lists the expected docking energy and other docking findings for the compounds.

Re-Rank Score	M. Dock Score	Interaction Data		Distance Annotation
		Enzyme Residue	Molecule atom	
-151.217	-90.5305	Thr 260 (O)	O-1	3.18 A°
		H_2O 87 (O)	O-1	2.60 A°
		H_2O175 (O)	O-2	3.03 A°
		Ser 252 (O)	O-3	2.84 A°
		His 78 (N)	O-4	3.04 A°
		H_2O 174 (O)	O-4	2.85 A°
		H_2O 174 (O)	O-5	3.27 A°

It also interacted with water molecules, which function as a strut between the oxygen and a enzyme residue in the target site, most likely H310 (Ji et al. 2000). It is thought that the higher the binding and lower the energy score, better the drug molecule's interaction to the target site and hence potency. As a result, the molecule works as a 14-demethylase inhibitor, which is accountable for the production of fungal cell walls. The inclusion of a hydroxyl group as a substituent enhances activity, according to the data (Rani & Singh, 2017; Rani, Kumar & Singh, 2019).

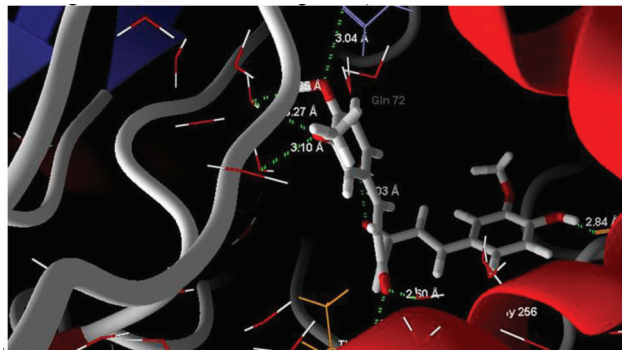

Figure 1: Curcumin binding mode in the target site of *Candida albicans* demethylase. Along with the distance, eight hydrogen bond interactions (with Thr 260, Ser 252, His 78, and five with H_2O molecules) were depicted. Enzyme's backbone is depicted as a ribbon shape.

Conclusion

Natural compounds' anti-Candidal potency was evaluated by a molecular docking research. The molecules were permitted to dock in the target site once it was imported and the target site was selected. Curcumin can function as a possible 14-demethylase inhibitor, according to a molecular modelling research, because it showed good to outstanding binding energy with enzyme residues and water molecules in the target site. To summarise, curcumin has the potential to be an essential chemical for further lead optimization. Furthermore, the presence of a hydroxyl function in a molecule results in a highly active chemical, according to the research.

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Authorship Contribution

Nidhi Rani: Manuscript drafting, data collection
Prerna Sharma: Supervision, software, investigation
Vikas Kumar Sharma: Editing, resources, manuscript writing
Praveen Kumar: Design, revision, visualization.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration

It is an original data and has neither been sent elsewhere nor published anywhere.

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