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In Silico Evaluation of Reserpine as Potential Anti-Candidal Agent

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ABSTRACT

Background: Candida *albicans* is a fungus that can cause mortality if not treated properly. Lanosterol 14α-demethylase produces Ergosterol, the main sterol in the fungal cell membrane, when the enzyme Lanosterol-demethylase is present (Cytochrome P450DM). This enzyme is a target enzyme for azole antifungal medications.

Purpose: In silico evaluation of reserpine as Potential Anti-Candidal agent.

Method: The target enzyme was chosen and modelled as part of the project. Molecular docking studies were used to investigate Reserpine's inhibitory impact on Cytochrome P450. MolegroVirtual Docker was used to conduct molecular docking and Chem sketch was utilised to build compound structures.

Result and conclusion: According to the docking research, reserpine exhibited interactions with the demethylase enzyme.

1. Introduction

Rauwolfia *serpentina* (Linne) Bentham ex Kurz. (Apocynaceae) is the dried root of Rauwolfia *serpentina* (Linne) Bentham ex Kurz. It is a tall shrub with cylindric stems that grows to a height of one metre. These stems contain a light-colored viscous latex and pale bark. Reserpine is the most significant alkaloid found in the plant's root, stem, and leaves. It includes at least 0.15 percent Reserpine-rescinnamine group alkaloids (calculated as Reserpine-rescinnamine group alkaloids)(Gawade and Fegade, 2012).

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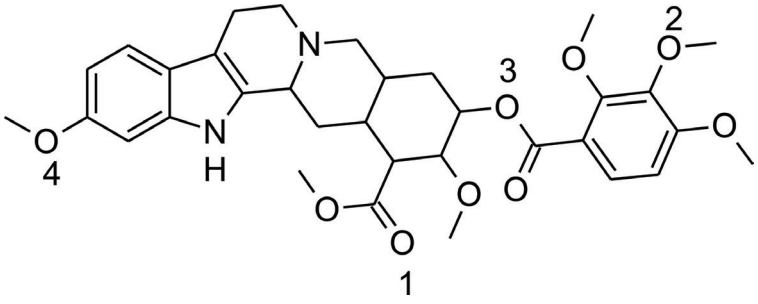

Antifungal medicines are commonly used to treat a range of fungal diseases (Menozzi *et al.,* 2004). They are treatments that selectively eliminate fungal pathogens from a host with little harm to the host. Bacteria acquire resistance to antifungal medications as a result of widespread usage, increasing the risk of severe infections (Gupta & coworkers, 2012; Rani & coworkers, 2015). The medications presently on the market for treating fungal infections have several drawbacks, including resistance and severe side effects. As a result, new antifungals that are both safe and efficacious have been developed (Arif, *et al.* 2009).

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The 14α-demethylase enzyme is involved in the synthesis of ergosterol, which is necessary for the formation of cell walls. As a result, the synthesis of fungal cell walls is prevented, and therefore fungus growth is impeded (Fromtling, 1988; Kitchen & coworkers, 2004)

From lead discovery through lead optimization, computational techniques are an integral component of the drug development process. Molecular modelling(Thomsen & Christensen, 2006) is one of the most widely used approaches for hit identification. The most aggressively valued molecule posture in the target binding is determined by this approach, which is based on energy ratings. The common consensus is that the lower the score, the better the enzyme-molecule interaction. As a consequence, the study may be used as an optimization tool to find the lowest-energy molecule-binding (Rani & coworkers, 2013). On undergoing the biological activity prediction it was found that the said compound exhibited some antifungal property. In continuation of our research on antifungals (Rani & Singh, 2018, 2019; Rani & coworkers, 2019, 2020) and the need for natural substances capable of eradicating fungal infections.

2. Materials and Methods

2.1. Docking Protocol

2.1.1. Ligand preparation

Chemical Sketch software, version 12.01, was used to sketch the structures of the chemicals identified in the factory under investigation. Using the same programme, the structures were 3D optimised.

2.1.2. Active site prediction

MVD software was used to investigate the microorganism's active location. The programme predicts five active sites, and one of the better locations was chosen for the docking process because it was closer to the cofactor and had the active ligand.

2.1.3. Protein selection

The 14-demethylase enzyme was used to test the antifungal efficacy of chemicals identified in the chosen plant. For this investigation, the protein with the pdb id 5TZ1 was chosen and retrieved from the Protein Data Bank (www.rcsb.org).

2.1.4. Docking and binding evaluation

The docking process was carried out using Molegro virtual docker (version MVD 2010.4.1.0).

2.2. ADME Study

The ADME research of the powerful compounds was carried out using an online platform, namely Swiss ADME software.

3. Results and Discussion

3.1. Docking Study

The docking research was conducted out using MVD software, which was entirely automated. The compounds that will be assessed were created in Chem sketch, 3D optimized, and then saved as mol files. The protein structure was constructed once the protein molecule was downloaded into the workspace. On the protein structure, a surface for molecules to bind was constructed, followed by cavity prediction. For docking prediction, the site that was closest to the co-factor and had the co-crystallized structure was chosen out of five. Following that, the ligand molecules were imported, which were also prepared and allowed to dock. The programme calculates the energy and chooses the optimum position with the maximum binding energy.

Table1. Docking Data for reserpine representing the interaction of the reserpine molecule with the amino acids of the enzyme.

Mol Dock Score	Re-rank Score	Interaction Data		Distance Annotation (H-Bond distance)
		Enzyme Residue	Molecule atom	
-133.037	-104.77	Tyr 76 (N)	O-1	3.24 A°
		Arg 95 (N)	O-2	3.56 A°
		Arg 95 (N)	O-2	3.56 A°
		Lys 99 (N)	O-3	3.06 A°
		H2O 174 (O)	O-4	3.15 A°

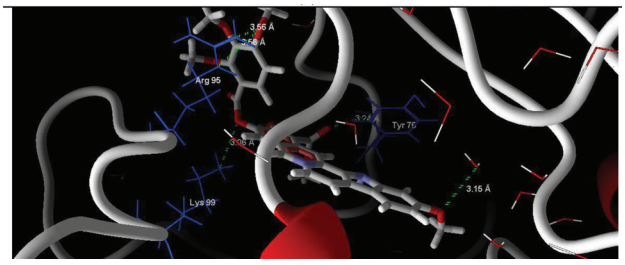

Figure 1: Binding Mode of Reserpine within the target site of the demethylase enzyme.

The docking study indicated that Reserpine exhibited interaction with the Tyr 76, Arg 95 and Lys 99 with -133.037 as dock score. This indicated that reserpine can

exhibited antifungal properties and can be used thereof. However, it also have interaction with water molecule which indicated indirect interaction of the drug molecule with the protein residue.

A molecule can only be turned to a medication if it has specific characteristics, which may be assessed using Swiss Dock online software (Rani & coworkers, 2012). Molecular property (including Molecular mass, logP, H-Bond acceptor, H-Bond donor, rotatable bonds, TPSA, and molecular refractivity), drug likeliness, medicinal chemistry, and pharmacokinetic profile of the compounds are all included in the programme.

3.2. Insilico ADME

Table 2: 3.2. Insilico ADME data.

A. Molecular Property								
Attributes	**Molecular Mass**	**Log P**	**H-Bond acceptor**	**H-Bond donor**	**Rotatable Bonds**	**TPSA**	**Molar Refractivity**	
	608.68	3.52	10	1	10	117.78	165.52	
B. Drug Likeliness								
Attributes	**Lipinski**	**Ghose**	**Veber**	**Egan**	**Muegge**	**Bioavailability Score**	*0Violation: Yes; 1-10 Violation: No	
	2	3	0	0	1	0.17		
C. Medicinal Chemistry								
Attributes	**Leadlikeliness**	**Synthetic Accessibility**	^ Synthetic accessibility: 1(very easy) 10 (very difficult)					
	3	5.95						
D. Pharmacokinetics								
GI absorption	**BBB permeation**	**Pgp substrate**	**CYP1A2 inhibitor**	**CYP2C19 inhibitor**	**CYP2C9 inhibitor**	**CYP2D6 inhibitor**	**CYP3A4 inhibitor**	**Log Kp**
High	No	Yes	No	No	No	No	No	-7.14

Conclusion

A molecular docking study was used to assess the anti-*Candida* efficacy of natural substances. Once the target site had been imported and the target site had been chosen, the molecules were allowed to dock there. According to molecular modelling studies, reserpine has good to excellent binding energy with enzyme residues and water molecules at the target region, making it a potential 14α-demethylase inhibitor. To summarize, reserpine has the potential to be an important molecule in the development of new lead compounds. According to the research, the presence of a hydroxyl function in a molecule results in a highly active chemical.

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Authorship Contribution

Nidhi Rani: Conceptualization, Methodology, Software, Writing- Reviewing and Editing.

Prerna Sharma: Data curation, Writing- Original draft preparation.

Rajwinder Kaur: Visualization, Investigation.

Praveen Kumar: Supervision, Software, Validation.

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None

Conflict of Interests

The authors declare no conflict of interests towards this paper.

Declaration

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

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