International Journal of Chemical Science
www.chemicaljournals.com
Online ISSN: 2523-2843, Print ISSN: 2523-6075
Received: 29-09-2025, Accepted: 28-10-2025, Published: 13-11-2025
Volume 9, Issue 2, 2025, Page No. 70-73

Molecular docking-based investigation of Abrine and Cirsimaritin for their antifungal potential

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Abstract
The present study employs a molecular docking approach to evaluate the interaction between selected bioactive compounds and the fungal target enzyme *Cytochrome P450 14α-demethylase* (CYP51A1), a key protein involved in ergosterol biosynthesis and fungal cell membrane formation. Molecular docking, an *in silico* computational technique, was utilized to predict the binding affinity and molecular interactions between the ligands and the target protein. The 3D structures of Abrine and Cirsimaritin were retrieved from
PubChem, while the receptor (CYP51A1) was obtained from the Protein Data Bank and prepared using PyMOL (version 2.3.4) by removing water molecules and heteroatoms followed by hydrogen addition. Docking simulations were performed using PyRx with the conjugate gradient algorithm for ligand optimization. The docking results revealed that Abrine exhibited a binding affinity of –7.2 kcal/mol, whereas Cirsimaritin demonstrated a stronger binding affinity of –8.5 kcal/mol with the active site residues of CYP51A1. These values indicate moderate-to-strong interaction potential, suggesting that both compounds possess promising antifungal properties through inhibition of the target enzyme. The findings support the potential of natural compounds from plant sources as lead molecules for antifungal drug development through *in silico* screening and molecular docking methodologies.

Keywords: Abrine, cirsimaritin, molecular docking, antifungal

Introduction

Abrine is an indole alkaloid predominantly isolated from *Abrus precatorius* Linn. seeds, known for its diverse pharmacological properties including antimicrobial, antioxidant, anti-inflammatory, and cytotoxic activities. Structurally, Abrine ($C_{11}H_{12}N_2O_2$) is a methyl ester derivative of tryptophan and acts as a bioactive secondary metabolite capable of interacting with various enzymatic targets through hydrogen bonding and π–π interactions. Previous *in silico* and *in vitro* studies have reported its potential as a natural inhibitor in several disease models due to its high binding affinity and stable molecular interactions with protein targets [1, 2].

Cirsimaritin is a naturally occurring flavonoid compound ($C_{16}H_{12}O_6$) widely distributed in plants belonging to the *Lamiaceae* and *Asteraceae* families. It exhibits multiple biological effects, including antioxidant, antimicrobial, anti-inflammatory, and anticancer properties. Cirsimaritin's structural framework, consisting of hydroxyl and methoxy functional groups, enables strong hydrogen bonding and hydrophobic interactions with enzyme active sites, contributing to its pharmacological activity. Recent molecular docking studies have shown Cirsimaritin's ability to bind effectively with cytochrome P450 enzymes and other oxidoreductases, suggesting its potential as an antifungal and anti-inflammatory agent [3, 4].

Molecular Docking Approach

The artificial intelligence tools used in silico study and bioinformatics discipline for drug discovery minimize the cost, time, and manpower. Molecular docking indeed plays an essential part in modern drug discovery and development. It enables researchers to explore the interactions between molecules, such as potential drug complexes and their target proteins, in a simulated environment.

A significant milestone in pharmaceutical research and development, establishing molecular docking as one of the most widely useful approaches in drug development and discovery. This surge in popularity was driven by technological advancements in experimental techniques such as NMR spectroscopy, X-ray crystallography, and protein-rich filtration methods, which provided detailed structural data essential for accurate docking simulations.

Molecular docking is a process that involves the interaction of molecules with receptors. It is a natural process that occurs in cells within seconds when they attach to form a stable complex. Molecular docking involves the use of computational techniques to predict the interaction between small molecules and their biological targets.

By estimating the binding affinities and poses [binding conformations] of these ligands within the active sites of target proteins, docking helps identify compounds that are likely to exhibit favorable binding energies, making them potential candidates for further development. The process involves generating and evaluating numerous potential binding conformations using scoring algorithms that assess the strength and stability of the interactions [5]

The basic requirements for molecular docking are as follows

- Ligand Representation

The structure that is most likely to be dominant is usually further modified by introducing or eliminating hydrogens, giving approximate pKa values.

Making sure that precise atom typing takes place is crucial

- **Receptor Representation**

The efficiency of docking calculations is significantly influenced by the superiority of the receptor structure used.

This suggests that better docking results will be observed at greater resolutions of the used crystal structure. A recent evaluation of the precision, constraints, and potential hazards of protein–ligand complex structure refinement procedures overall offered a critical appraisal of the existing structure.

Here are three types of molecular docking as follows

1. Rigid Docking

If we assume that molecules are stiff, we search for a transformation of one molecule in three dimensions that results in the best possible fit between it and another molecule in the form of a scoring function. It is possible to generate ligand conformation without a receptor or with a receptor-binding action present. Through database exploration, virtual screening is used to identify innovative drug candidates from a variety of chemical scaffolds

2. Flexible Docking

Assuming that molecules are flexible, our goal will be to identify receptor and ligand molecule conformations in addition to transformation.

3. Semiflexible docking

By using this tactic, the ligand molecules become the sole flexible components and the protein the only hard one. In addition to the six translational and rotational degrees of freedom, the conformational degrees of freedom of the ligand are also investigated. These techniques depend on a protein's fixed conformation to identify the ligands that require docking. The aforementioned statement is not always accurate [6].

Mechanisms involved in molecular docking

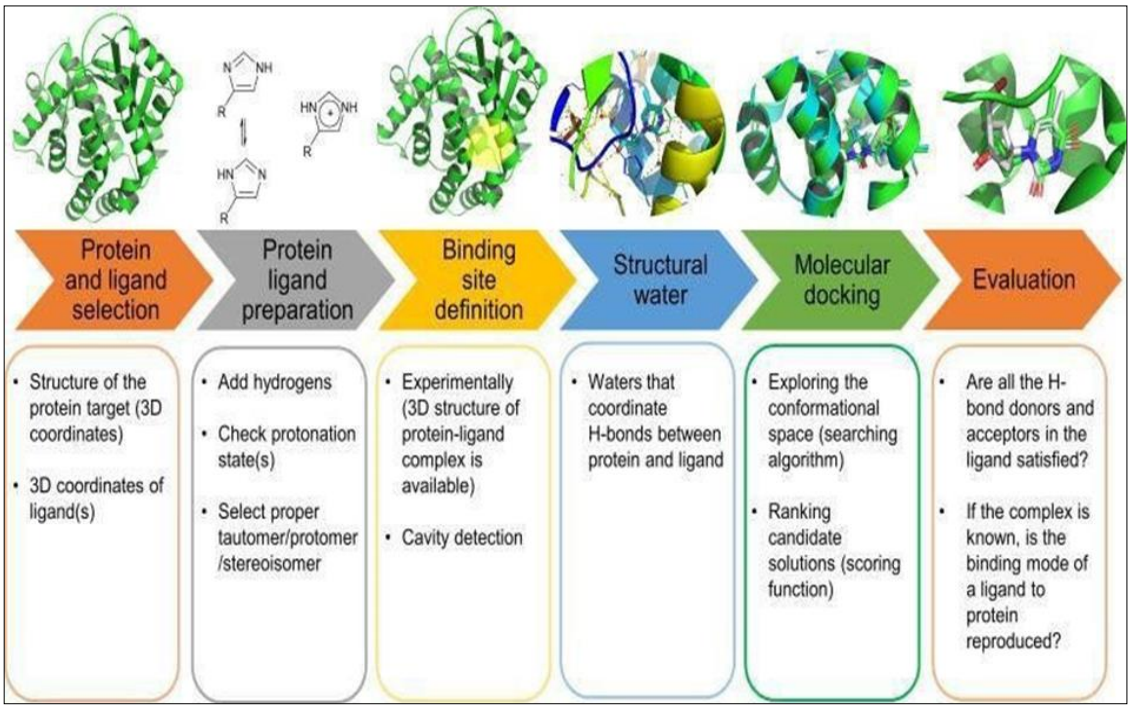

Fig 1: Mechanisms involved in molecular docking

Insilico Studies

- A computational technique used in drug discovery to predict the interaction between a ligand (small molecule) and a target protein. Helps in understanding binding affinity and molecular interactions.
- It is used to investigate how potential drug interact with proteins involved in acalculous Cholecystitis formation, such as those that influence crystal growth or matrix formation.

Molecular Docking in the Context of Anti-fungal Virtual Screening

Molecular docking is a virtual screening technique used to identify compounds that can bind to specific proteins involved in anti-fungal formation.

Target Identification: Researchers use docking to predict which proteins or molecules could be good targets for therapeutic intervention.

Drug Development: The predicted binding affinities and interactions can guide the design of new drugs or natural compounds that can inhibit fungal formation.

Mechanism of Action: Docking studies can help understand how a particular compound might work to prevent or reduce Anti-fungal formation.

Material and methods

Protein preparation

Preparation PyMoL version 2.3.4 was used for the receptor preparation. The crystal structure of Cytochrome P450 14α-demethylase (PDB ID: CYP51A1), which was generated from the Protein Data bank, was used for this investigation. The structure was cleaned from water and any hetero atom molecules, and then hydrogen atoms were added.

Ligand preparation

The 3D structure of the chemical constituents from the extracted plant were generated by PubChem. These structures are then prepared by Pymol by adding Hydrogen atoms. The ligands of Abrine and Cirsimaritin were studied

using the conjugate gradient algorithm in Open Babel of PyRx. 2.3.

Working Procedure

Target and Ligand Selection: Choose a macromolecule (protein) and a small molecule (ligand) for docking.

Websites: Protein data bank and PubChem

1. **Preparation:** Remove water molecules, add hydrogen atoms, and optimize structures.
2. **Grid Generation:** Define the active site where docking will occur.
3. **Docking Algorithm:** Simulates the interaction between ligand and protein using scoring functions.
4. **Scoring and Ranking:** Evaluates binding affinity and predicts the best binding mode.
5. **Analysis and Visualization:** Uses molecular visualization tools to interpret results.

Benefits of Molecular Docking

- **Early Identification of Promising Compounds**
  Docking can identify potential drug candidates before extensive and costly in vitro or in vivo testing.

- **Understanding Interactions**
  Docking reveals, the specific interactions between a molecule and a target protein, providing insights into the mechanism of action.

- **Cost-Effective**
  Molecular docking is a relatively inexpensive method compared to traditional experimental screening approaches [7, 8, 9].

Result and discussion

Insilico studies of abrine

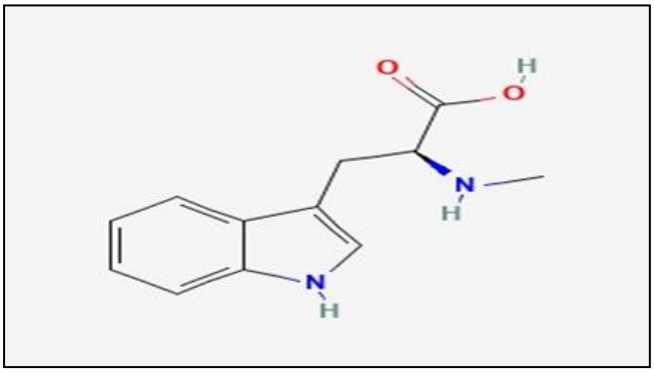

Fig 2: Structure Of Abrine

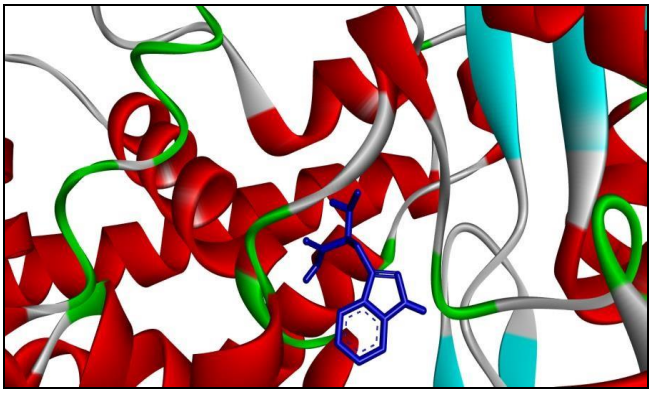

Fig 3 : Docked Molecule

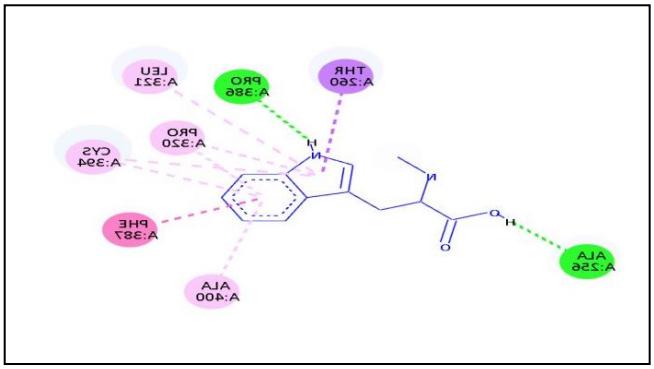

Fig 4: D Structure Of Aminoacid Interaction

The binding affinity of the tested compound/extract was found to be -7.2 kcal/mol.This value indicates a moderate level of interaction between the ligand and the target protein, suggesting that the compound has some degree of binding capability.

Insilico Studies Of Cirsimaritin

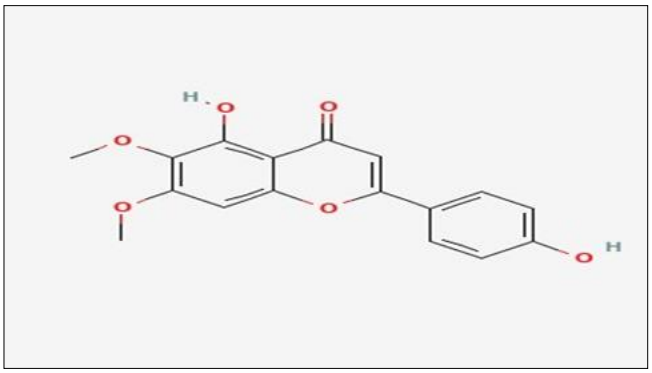

Fig 5: Structure Of Cirsimaritin

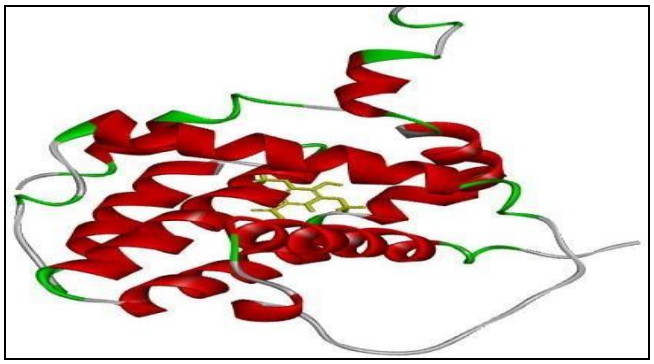

Fig 6: Docked Molecule

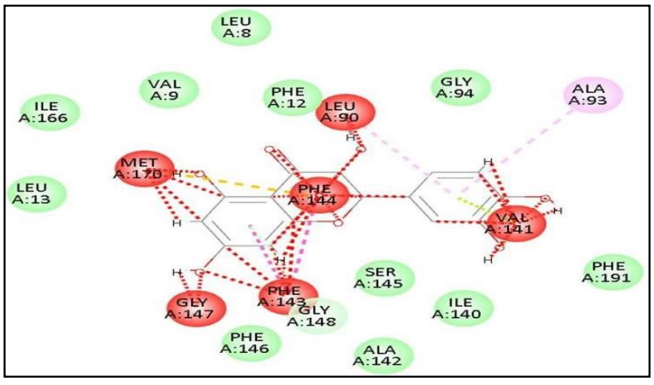

Fig 7: 2d Structure Of Aminoacid Interaction

The binding affinity of the tested compound/extract was found to be -8.5 kcal/mol.This value indicates a moderate level of interaction between the ligand and the target protein, suggesting that the compound has some degree of binding capability.

Discussion

- Binding affinity values closer to -10 kcal/mol or lower generally indicate strong binding, while values around -5 kcal/mol suggest moderate binding efficiency.
- The observed binding affinity (-7.2) and (-8.5) suggests that while the compound interacts with the target, the strength of this interaction is very high.

Acknowledgement

We express our deep sense of gratitude to Professor and faculty members of Department of Pharmaceutical chemistry, College of Pharmacy, Madurai Medical College for providing the guidance to carry out the studies.

Conclusion

The *in silico* molecular docking study successfully demonstrated the binding interactions of Abrine and Cirsimaritin with the fungal enzyme *Cytochrome P450 14α-demethylase* (CYP51A1). The observed binding affinities (–7.2 and –8.5 kcal/mol, respectively) indicate moderate to strong interactions, suggesting that both compounds can effectively fit within the enzyme's active site and potentially inhibit its activity. Among the tested ligands, **Cirsimaritin** showed higher binding potential compared to Abrine, indicating greater stability of the protein–ligand complex. The study emphasizes the importance of molecular docking as a costeffective and time-efficient computational strategy for identifying bioactive natural compounds with antifungal potential. Further *in vitro* and *in vivo* investigations are recommended to validate these docking results and confirm the pharmacological significance of these plant-derived molecules in antifungal therapy.

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