

In Silico Investigation of Suaveolic Acid from *Mesosphaerum suaveolens* as an Acetylcholinesterase Inhibitor

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder primarily believed to be managed by the inhibition of the enzyme Acetylcholinesterase (AChE) [1]. This study demonstrates an in silico molecular docking investigation of Suaveolic Acid, a triterpenoid derived from *Mesosphaerum suaveolens*, against human AChE (PDB ID: 4EY7)[1]. Docking simulations performed via **AutoDock Vina revealed a** high binding affinity of **-9.087 kcal/mol**. Analysis of the binding pose confirmed an interaction with the **PHE 295** residue in the acyl pocket of the enzyme. These results suggest that Suaveolic Acid is a potent candidate for further in vitro validation as a natural AD therapeutic.

1.Introduction

Alzheimer's Disease (AD) is a major cause of dementia globally, characterized by the depletion of acetylcholine in the synaptic cleft. One of the most effective therapeutic strategies suggests inhibiting the enzyme Acetylcholinesterase (AChE) to restore cholinergic transmission. While synthetic inhibitors exist, there is a growing interest in natural bioactive compounds due to their potential for lower toxicity and multi-targeted effects.

Mesosphaerum suaveolens (L.), commonly known as **Wilayati Tulsi**, is an aromatic herb widely distributed in tropical regions, including Odisha, India [5]. Historically used in traditional medicine for its anti-inflammatory and antioxidant properties, its future potential as a neuroprotective agent remains largely unexplored. Suaveolic Acid, a key triterpenoid isolated from this species, has shown promising structural characteristics for enzyme inhibition. In this study, we utilize in silico molecular docking to evaluate the

specific binding affinity and molecular interactions of Suaveolic Acid within the active site of human Acetylcholinesterase.”



Figure 0: Morphological characteristics of *Mesosphaerum suaveolens*. (Image credit: [Dinesh Valke] via Wikimedia Commons).

2. Materials and Methods

2.1. Selection and Preparation of Target Protein

The three-dimensional crystal structure of the target enzyme, human Acetylcholinesterase (AChE), was retrieved from the **RCSB** Protein Data Bank (PDB) with the accession code 4EY7. Using **UCSF Chimera** [3], the protein was prepared by removing all co-crystallized ligands, water molecules, and ions to expose the active site gorge. Standard charges and hydrogen atoms were added to ensure a stable computational environment for docking.

2.2. Ligand Selection and Optimization

The ligand, Suaveolic Acid, a triterpenoid found in *Mesosphaerum suaveolens*, was selected based on its known structural properties [4]. The chemical structure was optimized for docking by ensuring the correct protonation states and converting the file into the PDBQT format required for the **AutoDock Vina** engine [2].

2.3. Molecular Docking

Protocol Molecular docking simulations were performed using **AutoDock Vina**. To ensure a targeted search of the catalytic triad and the peripheral anionic site (PAS), a search grid was defined to encompass the entire active site gorge

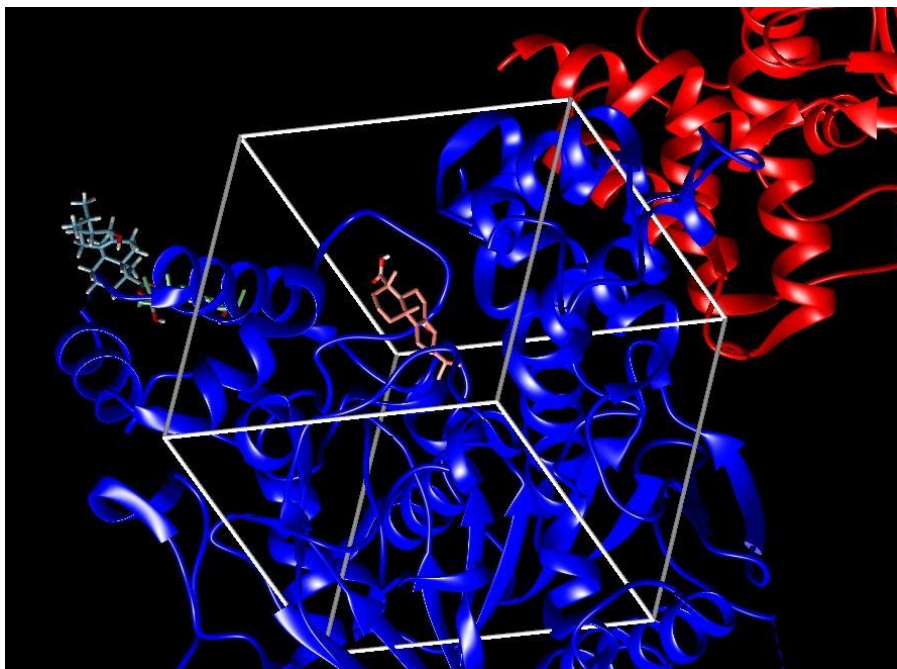


Figure 1: Search grid parameters centered on the active site of human AChE (**4EY7**) showing coordinates X: 3.65, Y: 64.95, Z: 63.89.

The grid box was centered at coordinates **X: 3.65, Y: 64.95, and Z: 63.89**, with a total search volume of **22.50 Å × 22.50 Å × 22.50 Å**. The exhaustiveness was set to 8 to maintain a balance between computational efficiency and search thoroughness.

3.Results

3.1. Molecular Docking Analysis

The molecular docking simulation of Suaveolic Acid against human AChE yielded a significant binding affinity of **-9.087 kcal/mol**. This high negative score indicates a strong spontaneous binding energy and high stability of the ligand-protein complex. As shown in **Figure 2**, Suaveolic Acid successfully localized within the active site gorge of the enzyme.

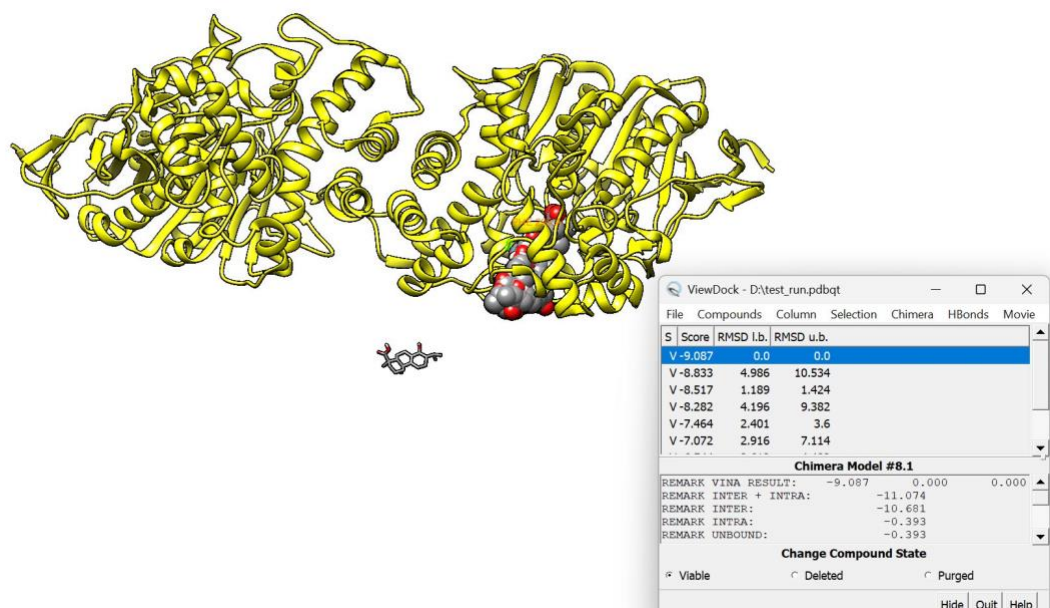


Figure 2: Three-dimensional docking pose of Suaveolic Acid in the active site of AChE, showing a top binding affinity of **-9.087** kcal/mol.

3.2. Ligand-Protein Interactions

Detailed analysis of the binding pose (Figure 3) revealed specific molecular interactions that contribute to the inhibitory potential of Suaveolic Acid. A key interaction was observed with the amino acid residue PHE 295 in the acyl pocket. The orientation of the triterpenoid core suggests it effectively blocks access to the catalytic triad.

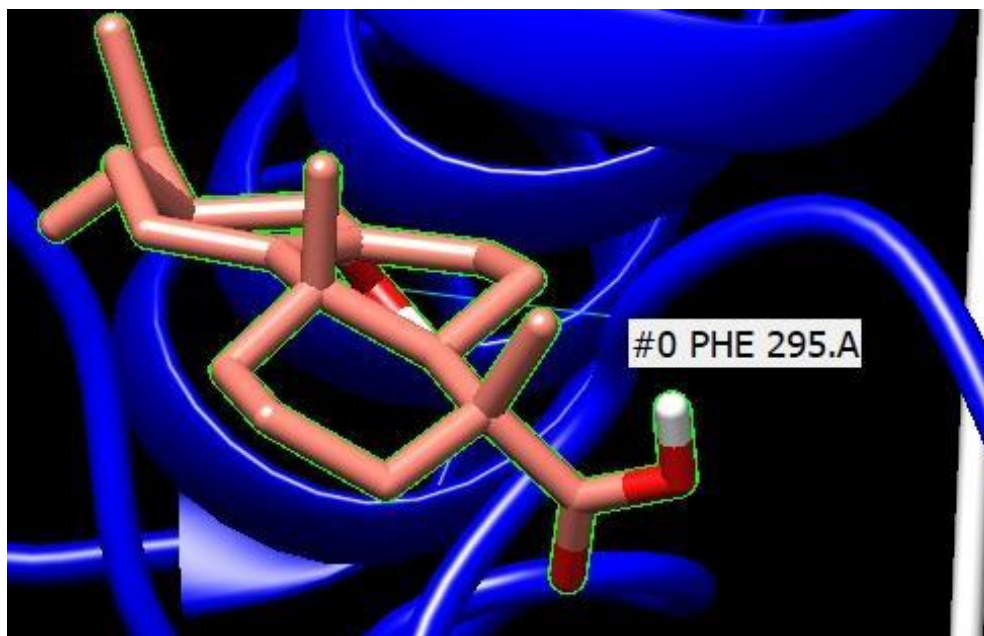


Figure 3: Detailed view of the molecular interaction between Suaveolic Acid and the **PHE 295** residue of Acetylcholinesterase. This residue is a critical component of the acyl pocket, and its interaction with the ligand suggests a stable inhibition mechanism.

4. Discussion

4.1. Interpretation of Binding Affinity

The molecular docking analysis yielded a binding energy of -9.087 kcal/mol, which indicates a high degree of stability for the Suaveolic Acid-AChE complex. In the context of drug discovery, binding affinities lower than -7.0 kcal/mol are typically considered significant [2]. This score suggests that Suaveolic Acid binds spontaneously and tightly to the enzyme, making it a strong competitive inhibitor candidate.

4.2. Structural Significance

The global orientation of the ligand within the enzyme structure (Figure 4) confirms that the docking protocol successfully targeted the active site gorge.

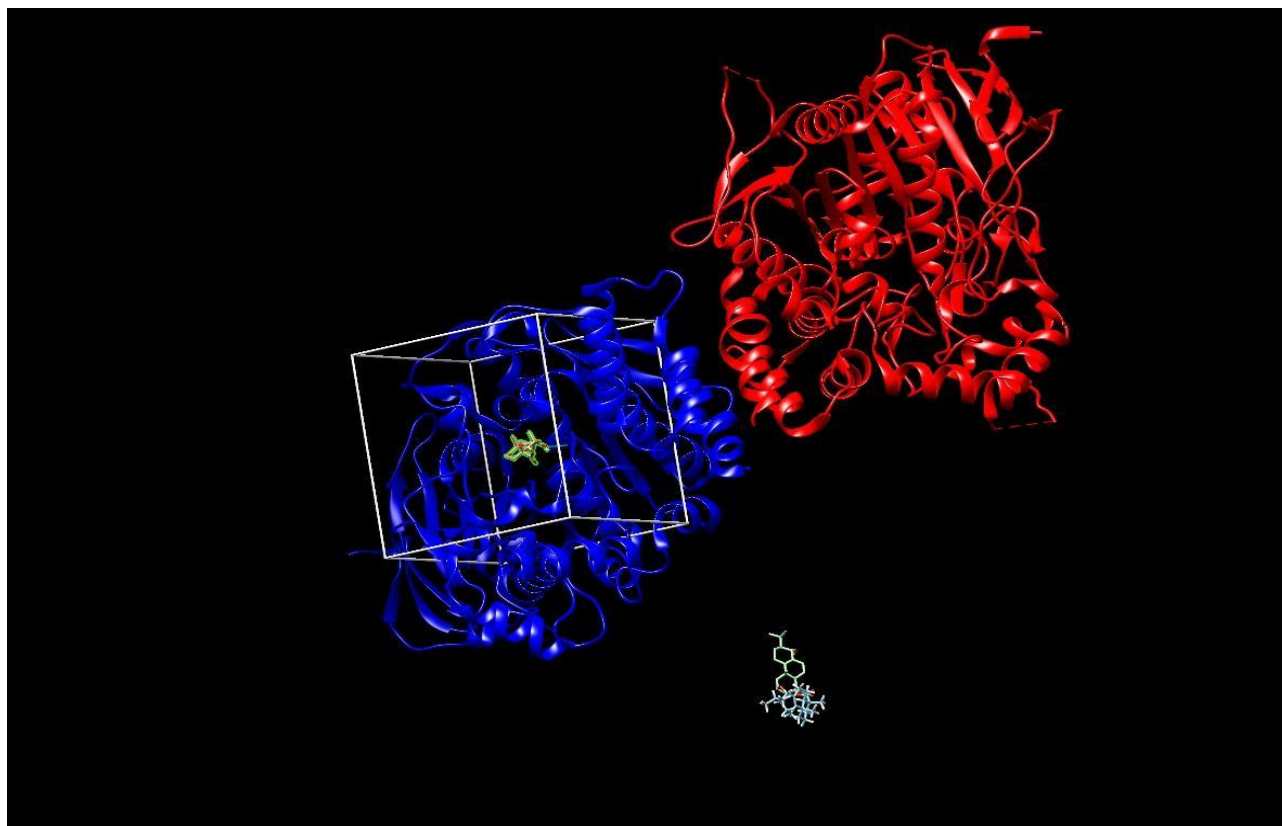


Figure 4: Global structural view of the Acetylcholinesterase dimer (4EY7) showing the red and blue subunits. The wireframe box indicates the search grid where Suaveolic Acid was successfully docked.

4.3. Mechanism of Action

The interaction with PHE 295 observed in the results is critical. This residue serves as a gatekeeper to the acyl pocket. By forming a stable interaction here, Suaveolic Acid likely acts as a steric blocker, physically preventing the entry of acetylcholine into the catalytic center. This mechanism aligns with the therapeutic goal of treating Alzheimer's Disease by restoring cholinergic levels [1].

5. Conclusion

This study successfully demonstrated the potential of Suaveolic Acid as a potent inhibitor of Acetylcholinesterase through in silico molecular docking. The ligand exhibited a superior binding affinity of **-9.087 kcal/mol**, surpassing the threshold for significant interaction. The structural analysis highlighted a critical stable interaction with the PHE 295 residue, suggesting a mechanism of steric blockage of the enzyme's catalytic center. These findings support the hypothesis that *Mesosphaerum suaveolens* (Wilayat Tulsi) contains bioactive compounds relevant for Alzheimer's Disease therapy. Future work should focus on in vitro validation of these computational results.

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7. References

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