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Short Communication

# Computational Analysis of β Carbolines Targeting Acetylcholinesterase Enzyme for Therapeutic Use in Alzheimer's Treatment

**Muhammad Sibte Hasan Mahmood***

*Department of Medicine, Grand River Hospital, 835 King St W, Kitchener, Canada*

## DESCRIPTION

This study revolves around therapeutic importance of natural alkaloids known as beta carbolines. Beta carboline belongs to a group of indole alkaloids and consist of pyridine ring that is fused to an indole skeleton. These alkaloids serve as the most promising candidates for the inhibition of acetylcholinesterase and can be used in the treatment of Alzheimer's disease. A detailed computational analysis of beta carboline alkaloids with acetylcholinesterase has been carried out using Molecular Docking method.

To accomplish the task, a ligand dataset of simple derivatives of beta carboline is constructed that includes Huperzine A, Galantamine, norharmane, Tryptoline, Pinoline, Harmane, Harmine and Harmaline. The 3D structure of acetylcholinesterase has been used as a receptor. The identification of binding site is a crucial step in validation of computational docking results. So, the crystal structure of acetylcholinesterase complexed with huperzine A (PDB ID: 4EY5) was retrieved from Protein Data Bank (PDB) as a reference to identify the binding residues. As huperzine A is an alkaloid possessing acetylcholine inhibition properties, its interaction with selected acetylcholinesterase residues could serve as binding pocket of the receptor. So, the binding site residues of this complex were analyzed using 2D interaction diagram via Ligplot. The residues involved in the interaction of crystallized structure of acetylcholinesterase with huperzine are Tyr133, Tyr119, Gly120, Gly126, Gly122, Ser125, Tyr337, Gly121, Tyr124, His447, Trp86, Ser203, Glu202. To verify the interacting residues, acetylcholinesterase was detached from huperzine A and again redocked. The post docking analysis revealed that residues involved in the interaction of crystallized structure of acetylcholinesterase with huperzine a were same as that of the residues obtained before redocking. Thus, this complex was taken as a reference and the interacting residues were correlated with the results of ligand dataset [1-5].

Correct identification of conserved binding site is pivotal in computational analysis. So, the conservation of acetylcholinesterase binding site across the species with different alkaloids was investigated. The retrieved pdbs included human AChE bound with huperzine A, AChE of pacific electric ray Torpedo californica bound with huperzine A and mouse AChE bound with huprine. The three structures were superimposed upon each other using Chimera and aligned structurally and sequentially. The conserved binding pocket residues were spotted across three species. It has been observed that the binding site is well conserved across the three species. This conservation of acetylcholinesterase binding pocket highlights the binding interaction between the receptor and ligand thus making it an important target for drug designing across the species.

After identification of correct binding site, rigid docking was performed i.e., the receptor undertaken in this study was studied in its static state rather than the dynamic state. The receptor, acetylcholinesterase was docked against the ligand dataset using Autodock 4.2. A total run of receptor with each respective ligand was set to 50 i.e., the ligand binds to its receptor in 50 different conformations and orientations. The grid size was set to cover the complete receptor thus allowing more space for the ligand to bind i.e., the ligand can bind anywhere on the receptor (blind docking). Ideally, the ligands were supposed to occupy the same binding site as that of the huperzine A with acetylcholinesterase [6-8].

After docking, the conformations were run based on the energy values; thus, the first structure corresponds to the lowest energy conformation. Post docking analysis showed that each ligand occupies the same binding site on acetylcholinesterase in its own respective orientation to form the most stable complex. However, each ligand is shown to bind to the same binding residues as reported in literature. The acquired residues were same as those of acetylcholinesterase huperzine a complex, thus validating the docking studies. The computational results can be validated further using in vitro approaches. The study supports that beta carbolines can be used as potent inhibitors against acetylcholinesterase for treatment of Alzheimer's disease.

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**Correspondence to:** Mahmood MSH, Department of Medicine, Grand River Hospital, 835 King St W, Kitchener, Canada, Tel: +1 (519) 716-7212; E-mail: dr.sibte@gmail.com

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