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Repurposing Studies of Curcumin for Alzheimer's Disease: A Comparative Study with Donepezil Using Molecular Docking

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ABSTRACT :

The present study evaluates the potential of curcumin as a repurposed therapeutic agent for Alzheimer's disease through comparative molecular docking studies with donepezil. Acetylcholinesterase (AChE), a key target involved in cholinergic neurotransmission, was selected for docking analysis. Curcumin and donepezil were docked against AChE to compare their binding affinity, interaction profile, and binding behavior within the catalytic active site (CAS) and peripheral anionic site (PAS). Curcumin demonstrated strong hydrogen bonding and aromatic interactions similar to donepezil, suggesting its potential as an AChE inhibitor. Although donepezil exhibited superior docking efficiency and pharmacokinetic optimization, curcumin showed promising dual-site interaction and neuroprotective potential. The study supports the possibility of repurposing curcumin for Alzheimer's disease management, though further in vitro and in vivo studies are necessary.

KEYWORDS: Curcumin, Donepezil, Alzheimer's disease, Molecular docking, Acetylcholinesterase, Drug repurposing.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and behavioral changes. The disease is associated with amyloid-β aggregation, phosphorylated tau fibril formation, oxidative stress, and cholinergic dysfunction. Acetylcholinesterase inhibitors such as donepezil remain standard symptomatic treatments for AD.

Drug repurposing has emerged as an efficient strategy for identifying new therapeutic uses for existing compounds. Curcumin, a natural polyphenol obtained from turmeric, possesses antioxidant, anti-inflammatory, and neuroprotective activities. The present study compares curcumin with donepezil which is a standard acetylcholinesterase inhibitor using molecular docking techniques to evaluate its potential as a repurposed drug candidate for Alzheimer's disease.

TARGET PROTEIN

Acetylcholinesterase (AChE) is a crucial enzyme in cholinergic neurotransmission. It rapidly hydrolyzes the neurotransmitter acetylcholine into acetate and choline, thereby terminating synaptic transmission at cholinergic synapses. The three-dimensional (3D) structure of AChE has been extensively studied using X-ray crystallography, providing insight into its catalytic efficiency and role in drug design.

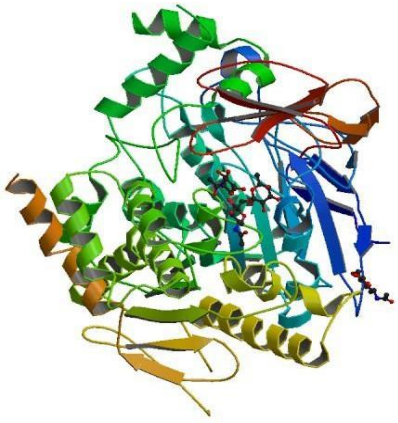


Fig 1.0 3D structure of acetylcholinesterase Mainly consists of 3 active sites, such as

1. **Deep and Narrow Active-Site Gorge**

Lined with aromatic amino acids (e.g., tryptophan, phenylalanine, tyrosine)**.** It guides acetylcholine to the catalytic site and contributes to extremely high catalytic efficiency

2. **Catalytic Triad**

Consist of serine histamine and glutamate residues which work together to hydrolyze acetylcholine through nucleophilic attack and formation of an acetyl-enzyme intermediate.

3. **Peripheral Anionic Site (PAS)**

Located at the entrance of the gorge which regulates substrate entry, involved in amyloid-β aggregation in Alzheimer's disease and is an important target for dual-binding inhibitor

MOLECULAR DOCKING

Molecular docking is a computational technique that predicts how a small molecule binds to a large biomolecule. It's used in drug design to help identify potential drug candidates and understand how they interact with proteins and other biomolecules. It is the study of how two or more molecular structures (eg; drug and enzyme or protein) fit together. In a simple definition, docking is a molecular modelling technique that is used to predict how a protein (enzyme)interacts with small molecules(ligands) The advantages of molecular docking is, time and economy saving, convenience, low cost, and also it is the key to rational drug design, and can identify the ligand's correct binding geometry in the binding site.

Docking helps in identifying potential drug candidates, understanding the mechanism of action and reducing the cost and time of experimental screening.

METHODOLGY: MOLECULAR DOCKING WORKFLOW

1. **Target Preparation** – Protein structure is obtained from Protein Data Bank and cleaned by removing water molecules, adding hydrogens, and assigning charges.
2. **Ligand Preparation** – Ligands are converted into optimized 3D structures with correct geometry and protonation states.
3. **Binding Site Identification** – The active site is determined based on experimental data or computational prediction.
4. **Grid Generation** – A 3D grid is defined around the binding site to guide docking calculations.
5. **Docking Simulation** – Ligands are placed into the binding site using algorithms to generate multiple conformations (poses).
6. **Scoring Function Evaluation** – Each pose is ranked based on predicted binding affinity (energy scores).
7. **Post-Docking Analysis** – Interactions between ligand and protein residues are analysed.
8. **Validation** – Docking accuracy is checked using RMSD or re-docking methods.
9. **Lead Optimization & Further Studies** – Promising compounds are refined and validated experimentally or via simulations.

3D BINDING MODEL OF CURCUMIN INSIDE ACHE

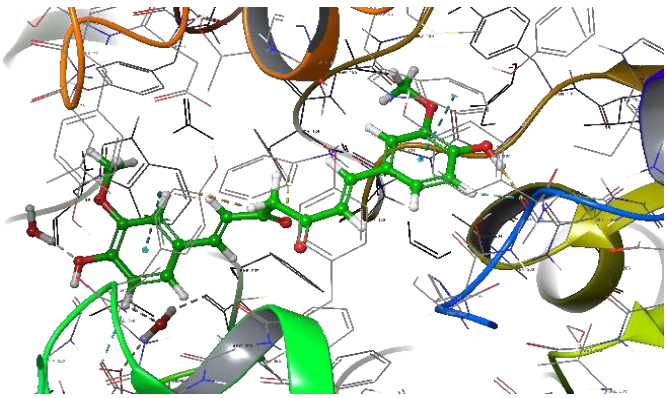


Fig 1.1 3D binding model of curcumin Docking score was found to be about -11.1kcal Mainly 3 kinds of interaction were seen in this docking such as,

A. Hydrogen Bonds

- Represented by dashed lines (cyan/yellow dashed lines).
- These are strong stabilizing interactions between ligand oxygen/nitrogen atoms, amino acid residues in the protein
- They increase binding affinity, stabilize ligand orientation and improve specificity

B. Hydrophobic Interactions

- Aromatic rings of the ligand interact with hydrophobic residues like , TRP (Tryptophan), LEU (Leucine) and PRO (Proline)
- They help the ligand remain buried in the binding pocket and are the major contributor to docking stability

C. π–π Stacking / Aromatic Interactions

- Aromatic rings of the ligand align with aromatic amino acids.
- Likely interactions with: TYR (Tyrosine) and TRP (Tryptophan)
- They stabilizes aromatic compounds such as donepezil or curcumin derivatives.

Interpretation of the Docking Pose

- The ligand is deeply embedded in the active site pocket
- Multiple hydrogen bonds are formed
- Aromatic and hydrophobic interactions stabilize the complex
- The binding orientation appears energetically favorable This generally indicates:

- good docking affinity
- stable ligand–protein interaction
- potential inhibitory activity

3D BINDING MODEL OF DONEPEZIL INSIDE ACHE

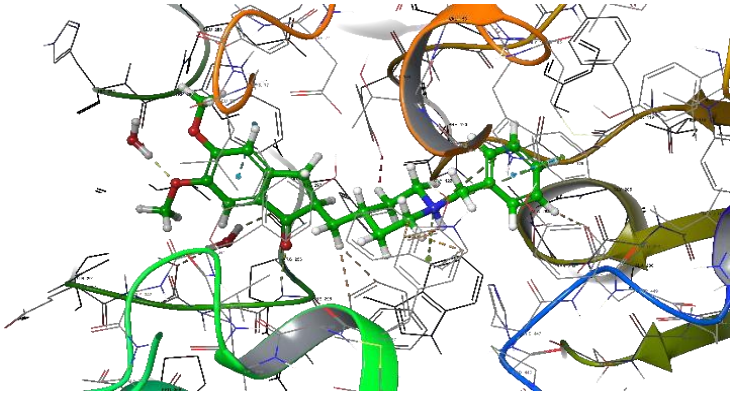


Fig 2.0 3d binding model of donepezil Docking score was found to be

-17.5 kcal Molecular interactions observed was ,

A. Hydrogen Bonding

- Shown by cyan dashed lines
- Formed between ligand oxygen/nitrogen atoms and amino acid residues.

It stabilizes ligand binding and improves specificity. Hydrogen bonds are essential for strong protein–ligand interaction**.**

B. Hydrophobic Interactions

The ligand contains aromatic and hydrocarbon regions interacting with nonpolar residues. Likely residues involved are TRP, LEU and PRO

These helps anchor ligand inside hydrophobic pocket and increases binding stability

C. π–π Stacking Interactions

Aromatic rings of the ligand interact with aromatic amino acids such as:

- TYR
- TRP

These interactions are very important in acetylcholinesterase inhibitors and aromatic drug molecules like donepezil or curcumin

INTERPRETATION

	CURCUMIN	**DONEPEZIL**
CAS binding	Yes	Yes
PAS binding	Yes	Yes
π–π stacking	Strong	Strong
Hydrogen bonding	Higher	Moderate
Flexibility	Higher	Optimised

CONCLUSION

The molecular docking study revealed that curcumin exhibits interaction patterns similar to donepezil against acetylcholinesterase. Curcumin demonstrated dual-site binding, hydrogen bonding, and aromatic interactions, suggesting its potential as a repurposed drug candidate for Alzheimer's disease.

However, limitations such as poor bioavailability and the need for experimental validation remain significant challenges. Further in vitro, in vivo, and pharmacokinetic studies are required to confirm its therapeutic applicability.

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