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Computational Analysis of Huperzine A as a Natural Acetylcholinesterase Inhibitor in Alzheimer's Disease

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Abstract:
Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and memory impairment. Acetylcholinesterase (AChE) inhibitors are widely used for the symptomatic treatment of AD by increasing acetylcholine concentration in the synaptic cleft. The present study evaluates the phytochemical Huperzine A as a potential AChE inhibitor using molecular docking techniques. The three-dimensional structure of AChE was obtained from the Protein Data Bank (PDB), while the ligand structure of Huperzine A was retrieved from the PubChem database. Molecular docking was performed using Pyrx software to determine binding affinity and molecular interactions. The docking analysis demonstrated strong binding interactions between Huperzine A and the active site residues of AChE with favourable binding energy. The Visualization and Analysis performed using Discovery Studio. Hydrogen bond interactions and hydrophobic contacts contributed to the stability of the ligand–protein complex. ADMET analysis further indicated acceptable pharmacokinetic properties and drug-likeness. The results suggest that Huperzine A may serve as a promising natural acetylcholinesterase inhibitor for the management of Alzheimer's disease.

Keywords: Alzheimer's disease, Huperzine A, Acetylcholinesterase, Molecular Docking, Phytochemical.

INTRODUCTION

It is the most prevalent form of dementia which does not have any previous cause like stroke, brain trauma or alcohol toxicity. The symptoms of AD are progressive loss of memory and disordered cognitive functions, with loss of short-term memory that usually preceeds loss of long-term memory. Patients of AD may not recognise their own family members. Other signs include reduced verbal fluency and impairment of speech due to failure of arranging words in proper sequence. Ultimately, patient may fall in to a vegetative state. Death is usually associated with complications of immobility; e.g. pneumonia or pulmonary embolism. The loss of cholinergic activity in brain or patients with AD led to the use of cholinesterase inhibiting drugs which can cross BBB. These drugs block degradation of AChE and increase availability of AChE in synaptic cleft. The drugs used to treat AD are: Tacrine, Donepezil, Rivastigmine and Galantamine. Tacrine is a long-acting reversible anticholinesterase. It can be used for treatment of mild to moderate patients of AD. It is orally active and provides improvements in memory, cognition and general well being soon after initiation. It facilitates release of AChE from cholinergic nerve ending. However, it produces significant hepatotoxicity hence its use is restricted. Donepezil, Rivastigmine and Galantamine have better penetration in CNS. They are less toxic and better tolerated in comparison to Tacrine. Their clinical results are modest and temporary. [1]

AD accounts for 60–80% of cases and 1.9% relative risk and prevalence. Nearly 1 in 3 adults suffer from multiple chronic conditions globally. In the year 2008 as a part of the "Mental health Gap Action Programme" (MH GAP), the world health Organisation (WHO) declared dementia as a priority condition. The theme for MH GAP Forum 2018 is Accelerating Countries' Action on Mental Health. According to

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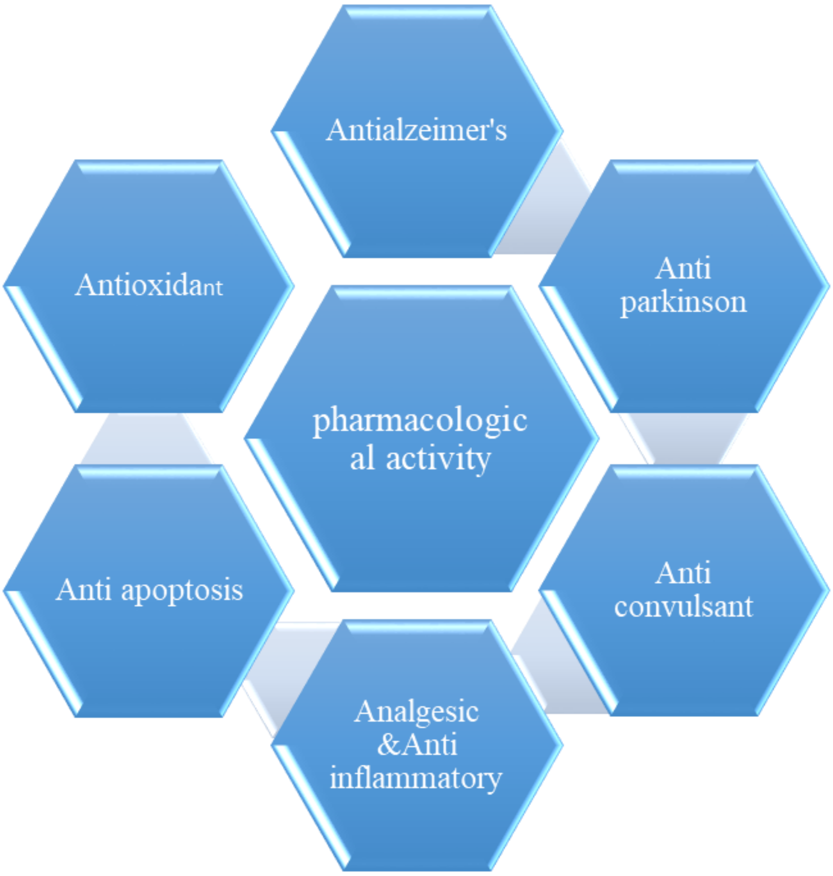
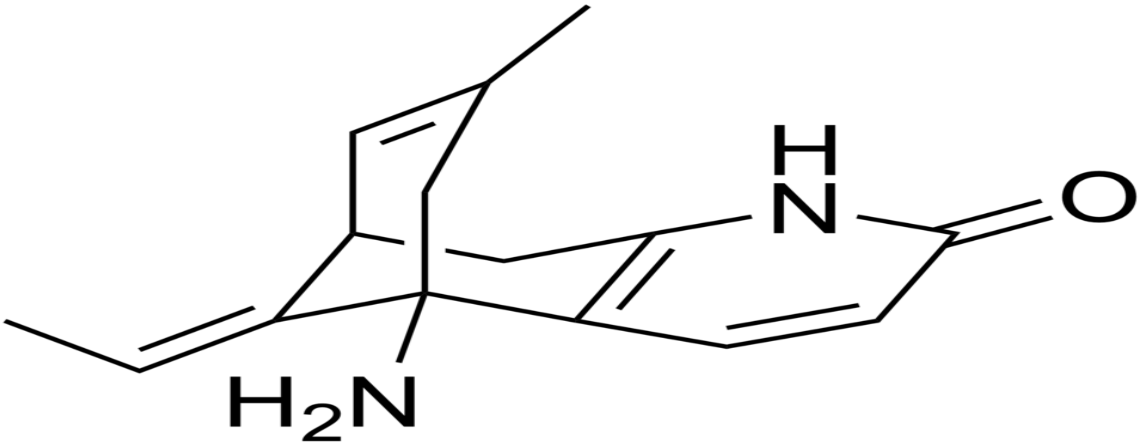
a report, Berea et al. Int. J. Pharm. Res. Allied Sci., 2021, 10: 110-120 111 there could be an increase of 35% of new AD cases in the next 20yrs That approximates the total number of new dementia cases annually worldwide is nearly 7.7 million that is defining a fresh case for every 4 sec. In 2015 the prevalence is 4.4 million, which estimates to be doubled by 2050. The incidence of AD is in increasing order as, Asia, Europe, and North America. 1-6% of recorded cases are of the age 30-60 which is termed as an early-onset disease. The mortality increases as the disease progress. In India, the order of prevalence of AD is West India, South India, North India, and East India in order.[2]

HUPERZINE A



[3]

Huperzine A, the active ingredient derived from the traditional Chinese herb, is an efficacious, selective, and reversible acetylcholinesterase inhibitor (AChEI) and has been used to combat fever, inflammation, blood disorders, schizophrenia, cognitive dysfunction, and dementia.[4]
During neurotransmission, the neurotransmitter acetylcholine (AChE) released from the presynaptic nerve binds to the corresponding receptor. At the postsynaptic membrane, acetylcholine is hydrolyzed to acetate and choline by acetylcholinesterase to terminate the relay of the neurotransmission. [5]
Importance in Alzheimer's Disease of Huperzine A it improves cholinergic neurotransmission and reduces cognitive decline associated with Alzheimer's disease. Due to its high selectivity and blood-brain barrier penetration, it is considered a promising phytochemical for neurodegenerative disorders.[6]



[7]

AIM

To evaluate the therapeutic potential of phytoconstituents against Alzheimer's disease through molecular docking studies by analysing their binding affinity and interaction with target proteins involved in the disease pathology.

OBJECTIVES

1. Selection of Phytoconstituents

To identify and select phytoconstituents from medicinal plants reported to possess neuroprotective, antioxidant, anti-inflammatory, or anti-cholinesterase activities through literature survey and phytochemical databases.

Explanation

Medicinal plants contain several secondary metabolites such as:

- Alkaloids
- Flavonoids
- Terpenoids
- Phenolic compounds
- Glycosides

These compounds may help in reducing neuronal degeneration associated with Alzheimer's disease.

Examples of commonly studied phytoconstituents:

- Curcumin
- Quercetin
- Galantamine
- Resveratrol
- Huperzine A

2. Identification of Alzheimer's Disease Target Proteins

To select important molecular targets associated with the progression of Alzheimer's disease for docking analysis.

Major Target Proteins

- Acetylcholinesterase (AChE)
- Butyrylcholinesterase (BuChE)
- Beta-secretase enzyme (BACE1)
- Glycogen synthase kinase-3 beta (GSK-3β)
- Tau protein
- Amyloid-beta peptide

Explanation

These proteins are involved in:

- Breakdown of acetylcholine neurotransmitter
- Formation of amyloid plaques
- Neurofibrillary tangles
- Neuronal cell death

Inhibiting these targets may slow disease progression and improve cognitive function

3. Preparation of Ligands and Protein Structures

To prepare the three-dimensional structures of selected phytoconstituents (ligands) and target proteins for molecular docking studies.

Explanation

This objective includes:

- Downloading ligand structures from databases such as:
  - PubChem
  - ChemSpider
- Obtaining protein crystal structures from:
  - Protein Data Bank (PDB)
- Energy minimization of ligands
- Removal of water molecules and unwanted residues from proteins
- Addition of hydrogen atoms and charges

This preparation improves docking accuracy.

4. Molecular Docking Analysis

To perform molecular docking of selected phytoconstituents with Alzheimer's disease target proteins using computational docking software.

Common Docking Software

- AutoDock
- AutoDock Vina
- PyRx
- Schrödinger
- Discovery Studio

Explanation

Docking helps predict:

- Binding orientation
- Binding affinity
- Interaction strength
- Stability of ligand–protein complex

The docking score indicates how strongly the phytoconstituent binds to the target protein.

5. Evaluation of Binding Interactions

To analyze molecular interactions between phytoconstituents and target proteins based on docking results.

Parameters Studied

- Binding energy
- Hydrogen bonding
- Hydrophobic interactions
- Electrostatic interactions
- Van der Waals forces

Explanation

Strong and stable interactions suggest better inhibitory potential against the target protein.

Lower binding energy generally indicates:

- Better binding affinity
- Higher stability
- Greater biological activity

6. Comparison with Standard Drugs

To compare the docking results of phytoconstituents with standard anti-Alzheimer drugs.

Standard Drugs Commonly Used

- Donepezil
- Rivastigmine
- Galantamine
- Memantine

Explanation

This comparison helps determine whether natural compounds show:

- Similar binding efficiency
- Better interaction profiles
- Potential as safer alternatives with fewer side effects

7. Prediction of Drug-Likeness and ADMET Properties

To evaluate pharmacokinetic and toxicity profiles of selected phytoconstituents using in silico ADMET analysis.

Parameters Evaluated

- Absorption
- Distribution
- Metabolism
- Excretion
- Toxicity

Common Rules

- Lipinski's Rule of Five
- Bioavailability prediction

Explanation

This objective helps identify compounds with:

- Good oral bioavailability
- Low toxicity
- Favorable drug-like properties

8. Identification of Lead Molecules

To identify the most promising phytoconstituents based on docking score, interaction pattern, and pharmacological properties for further experimental studies.

Explanation

Lead compounds identified through docking studies may be further evaluated by:

- In vitro studies
- In vivo studies
- Clinical research

This may contribute to the development of novel plant-based therapeutics for Alzheimer's disease.[8]

MATERIALS

Materials

1. Hardware Requirements: Computer/Laptop
2. Operating System: Windows / Linux / macOS
3. Software Requirement
   - PyRx (main docking platform) & PyMol
   - Discovery Studio Visualizer – for interaction analysis
   - Open Babel – for format conversion (SDF to PDB, etc.)
4. Online Database:

   PubChem – to download Huperzine A structure

   Protein Data Bank (RCSB PDB) – to obtain 3D structure of AchE protein for Molecular Docking

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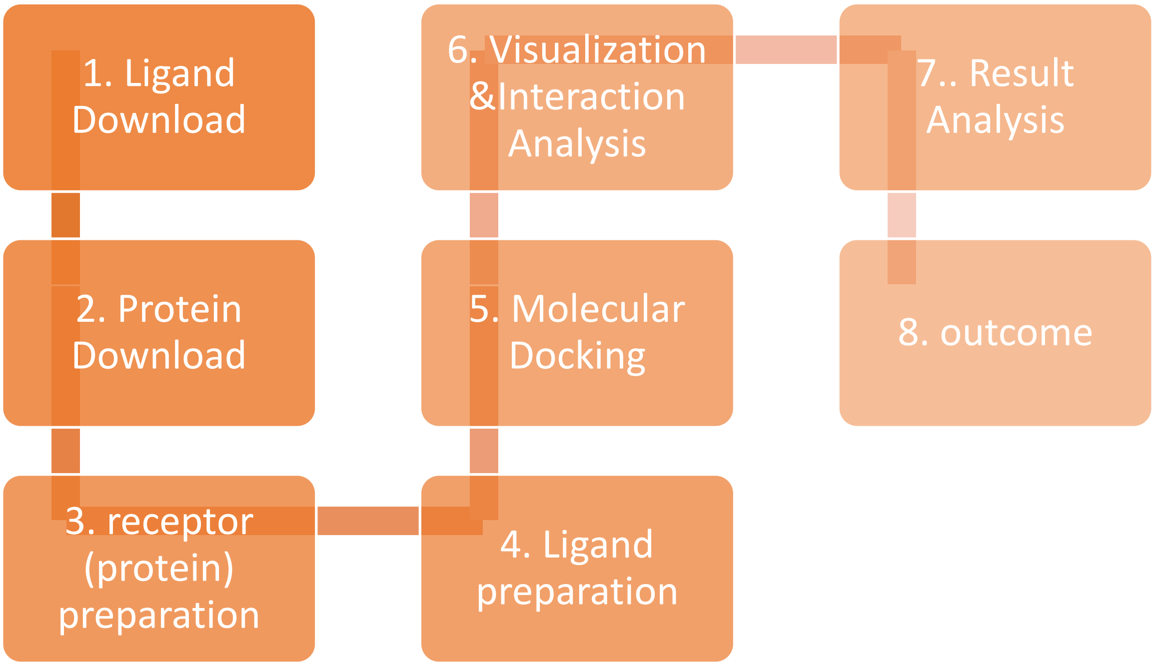
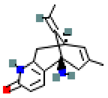
METHODOLOGY



1.Ligand Download:

Open PubChem website by searching the keyword "Huperzine A" or using its PubChem CID 854026. After accessing the compound page, the structure can be downloaded from the download section in SDF format. This downloaded ligand file is then further processed and converted into appropriate formats (such as PDB and PDBQT) for molecular docking analysis.



Huperzine A; (-)-huperzine A; 102518-79-6; (-)-huperazine A; L-huperzine A; ...

Compound CID: 854026

MF: $C_{15}H_{18}N_2O$ **MW:** 242.32 g/mol

IUPAC Name: (1R,9R,13E)-1-amino-13-ethylidene-11-methyl-6-azatricyclo[7.3.1.02,7]trideca-2(7),3,10-trien-5-one

SMILES: C/C=C/1\\[C@@H]2CC3=C([C@]1(CC(=C2)C)N)C=CC(=O)N3

InChIKey: ZRJBHWIHUMBLCN-YQEJDHNASA-N

InChI: InChI=1S/C15H18N2O/c1-3-11-10-6-9(2)8-15(11,16)12-4-5-14(18)17-13(12)7-10/h3-6,10H,7-8,16H2,1-2H3,(H,17,18)/b11-3+/t10-,15+/m0/s1

Create Date: 2005-06-24

2. Protein Download:

Open Protein Data Bank website the three-dimensional structure of this protein is obtained from the Protein Data Bank. The retrieval process involves accessing the PDB website and searching for "AchE" which provides multiple structural entries. Among these, well-characterized and widely used structures such as 4EY7, are recommended due to their good resolution and reliability for docking studies. protein structure is downloaded in PDB format using the download option provided on the website. This downloaded file serves as the primary input for subsequent protein preparation and molecular docking analysis in the study1. Receptor Preparation (Discovery Studio)

3.Receptor Preparation

the target protein acetylcholinesterase (AChE) was obtained from the Protein Data Bank (PDB) in .pdb format. The protein structure was imported into Discovery Studio for receptor preparation. During preparation, all unwanted water molecules present in the protein structure were removed to avoid interference during docking. Heteroatoms and co-crystallized ligands already bound to the protein were also deleted. Hydrogen atoms were then added to stabilize the protein and maintain proper valency and

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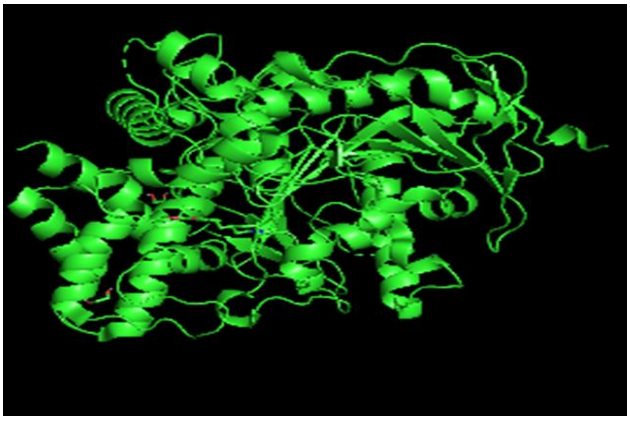
protonation states. After hydrogen addition, the geometry of the protein was cleaned and optimized to remove steric clashes and structural irregularities. The prepared receptor was finally saved in .pdb format for docking studies.

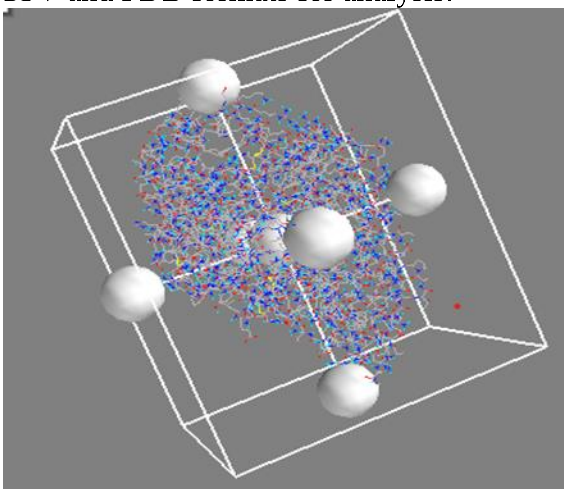


4. Ligand Preparation

Save ligand as ligand. Pdbqt for ligand preparation, selected phytochemicals with potential anti-Alzheimer activity were collected from chemical databases such as PubChem in .sdf format. The ligand structures were imported into PyRx software using Open Babel. Energy minimization was performed using the “Minimize All” or “Minimize Selected” option to obtain stable conformations with minimum energy. After minimization, the ligands were converted into. pdbqt format, which is required for Auto Dock Vina docking. The prepared ligand files were then saved for further analysis.

5.Molecular Doccking

Molecular docking studies were performed using PyRx integrated with AutoDock Vina. The prepared receptor and ligand files were loaded into the Vina Wizard. A grid box was defined around the active site of acetylcholinesterase to ensure that docking occurred specifically at the catalytic region of the enzyme. Important active site residues such as Ser203, His447, Tyr337, Trp86, Glu334, and Phe338 were considered while setting the grid dimensions. Docking simulations were then executed using AutoDock Vina. After completion of docking, different binding poses along with binding affinity values expressed in kcal/mol were generated. The docking pose showing the lowest binding energy was selected as the best model because lower energy indicates stronger and more stable binding between ligand and receptor. The docking results were saved in CSV and PDB formats for analysis.



6. Visualization and Interaction Analysis (Discovery Studio)

Ser203, His447, Tyr337, Trp86, Phe338, Glu334 The docked complexes were further analyzed using Discovery Studio for visualization and interaction studies. The prepared protein structure was opened first, followed by the docked ligand structure representing the best docking pose. The ligand was inserted into the protein binding site for detailed interaction analysis. Various molecular interactions between ligand

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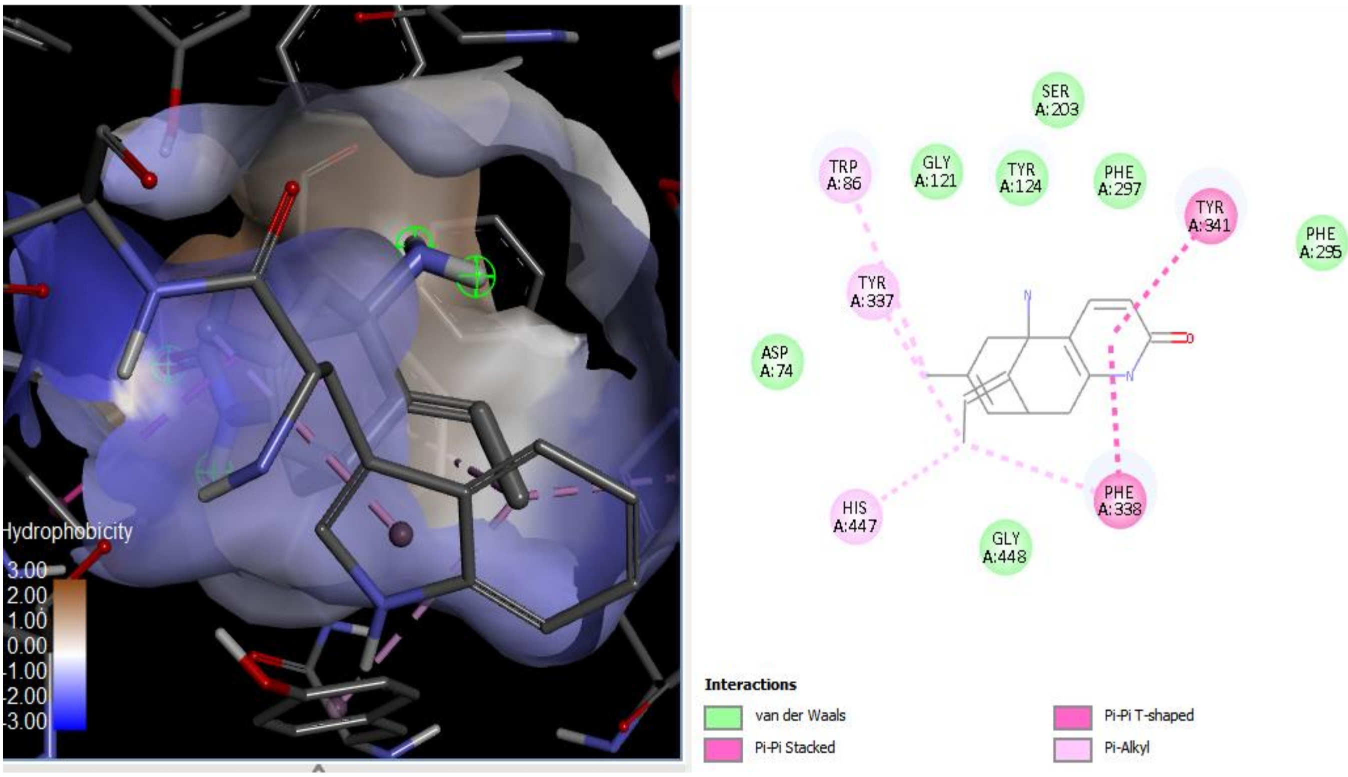
and protein residues were examined, including hydrogen bonding, hydrophobic interactions, π–π interactions, and Van der Waals forces. Special attention was given to interactions occurring with catalytic and active site residues of acetylcholinesterase because these interactions are important for inhibitory activity. Two-dimensional and three-dimensional interaction diagrams were generated to visualize the binding pattern clearly.



7. Result Analysis

Finally, result analysis was performed by recording the binding affinity values of all phytochemicals. The interacting amino acid residues and types of molecular interactions were carefully noted. The hydrogen bonding patterns and hydrophobic interactions were compared among different compounds. Phytochemicals showing lower binding energy and strong interactions with key active site residues were considered as potential acetylcholinesterase inhibitors for the treatment of Alzheimer's disease. The overall outcome of the study was the identification of promising phytochemicals with significant inhibitory potential against acetylcholinesterase enzyme.

8. ADMET Prediction

The ADMET prediction of Huperzine A was performed using the SwissADME online tool. Initially, the SMILES structure of Huperzine A was obtained from the PubChem database. The compound name was searched in PubChem, and the canonical SMILES notation was copied from the compound information page.The copied SMILES string was then pasted into the input box of SwissADME. After submitting the structure, the software generated pharmacokinetic and drug-likeness parameters including molecular weight, hydrogen bond donors and acceptors, lipophilicity (LogP), gastrointestinal absorption, blood–brain barrier permeability, and Lipinski's Rule of Five.The obtained ADMET results were analyzed to evaluate the drug-likeness, bioavailability, and pharmacokinetic behavior of Huperzine A for its potential application in Alzheimer's disease treatment.[9-14]

PLAN OF WORK

Introduction

Molecular docking is a computational approach used to predict the interaction between bioactive compounds and target proteins for drug discovery studies.

The study involves protein and ligand preparation, active site identification, molecular docking analysis, and interaction visualization using computational software to determine the binding affinity and stability of the Huperzine A - AchE complex. The findings of this study may contribute to the development of natural anti-tubercular agents for future therapeutic applications.

Molecular Docking procedure

The molecular docking procedure involves several steps:

1.Selection of Target Protein (download structure from the Protein Data Bank (PDB)
2. Ligand Selection and Preparation (download phytochemicals form the PubChem)
3. Grid Box Generation (Setting the docking area around the active site for ligand binding analysis.)
4. Molecular Docking Simulation (Performing docking using software)
5. Interaction Analysis
6. Visualization of Docked Complex (Visualization of 2D and 3D protein–ligand interactions)
7. Result Interpretation

Analysis of Phytochemical Active Binding Site

The molecular docking analysed for phytochemical Active site of Target Protein:
The following points are analysed in active site:

1. Binding Affinity / Docking Score (The docking score (kcal/mol) indicates the strength of interaction between the phytochemical and the target protein. A more negative value represents stronger and more stable binding.)
2. Hydrogen Bond Interactions (Hydrogen bonds formed between the ligand and amino acid residues of the protein are analysed)
3. Hydrophobic Interactions
4. Amino Acid Residues Involved
5. RMSD Value
6. Visualization of 2D and 3D Interactions

Molecular Docking Perform

Molecular Dockimg performs importance:

1. Prediction of Ligand–Protein Interaction Molecular docking helps in predicting the interaction between a ligand and the target protein at the molecular level, which is essential for understanding the mechanism of drug action.
2. Identification of Binding Affinity evaluates the binding affinity and stability of the ligand–protein complex through docking scores and binding energy values.
3. Active Site Analysis Docking assists in identifying the active binding pocket and important amino acid residues involved in molecular interactions.
4. Drug Discovery and Development Molecular docking plays a significant role in computer-aided drug design by screening potential compounds before experimental studies.
5. Reduction of Experimental Cost and Time silico docking studies reduce laboratory workload, experimental cost, and time by selecting the most promising compounds for further investigation.
6. Prediction of Drug Efficacy Docking studies help in predicting the biological activity and effectiveness of compounds against specific targets.
7. Structure-Based Drug Design The optimization and modification of lead compounds for improved binding and pharmacological activity.

8. Visualization of Ligand Orientation helps visualize the orientation and conformation of the ligand within the protein binding cavity.
9. Improvement of Research Accuracy Molecular docking increases the reliability and scientific accuracy of pharmaceutical and biochemical research studies.

Molecular Docking Perform Using the Following Software's:

1. PyRx (main docking platform)
2. PyMOL – for 3D structure visualization & protein preparation
3. Discovery Studio Visualizer – for interaction analysis
4. Open Babel – for format conversion (SDF to PDB, etc.)
5. PubChem – to download Huperzine A structure
6. Protein Data Bank (RCSB PDB) – to obtain 3D structure of AchE protein[15]

SUMMARY

The present study was conducted to investigate the molecular docking interaction of the phytochemical Huperzine A against the acetylcholinesterase (AChE) target protein associated with Alzheimer's disease to evaluate its potential neuroprotective and anti-Alzheimer activity. Alzheimer's disease is a progressive neurodegenerative disorder characterized by memory loss, cognitive impairment, and reduced cholinergic neurotransmission. The inhibition of acetylcholinesterase helps in increasing acetylcholine levels in the brain, thereby improving cognitive function and neuronal communication.

Huperzine A, a bioactive alkaloid isolated from Huperzia serrata, was selected for this study because of its reported acetylcholinesterase inhibitory activity, neuroprotective properties, antioxidant effects, and comparatively lower toxicity. In recent years, phytochemicals have attracted considerable attention in drug discovery due to their therapeutic potential and natural origin.

The three-dimensional crystal structure of the acetylcholinesterase target protein was obtained from the Protein Data Bank (PDB), while the chemical structure of Huperzine A was retrieved from the PubChem database. The ligand and protein structures were prepared and optimized prior to molecular docking analysis using appropriate computational tools and docking software. The docking study was performed to analyze binding affinity, hydrogen bonding, hydrophobic interactions, amino acid residue interactions, and ligand–protein complex stability.

The molecular docking results revealed that Huperzine A exhibited strong binding affinity toward the active binding pocket of the acetylcholinesterase protein, suggesting the formation of a stable ligand–protein complex. Interaction analysis demonstrated the involvement of significant amino acid residues through hydrogen bonding and hydrophobic interactions, which contributed to the stabilization of the docked complex.

Furthermore, the 2D and 3D interaction studies confirmed the effective orientation and proper accommodation of Huperzine A within the active site region of the acetylcholinesterase protein. These interactions indicated the potential inhibitory activity of Huperzine A against acetylcholinesterase enzyme activity.

Huperzine A possesses promising inhibitory potential against the acetylcholinesterase target protein and may serve as a potential lead molecule for the development of safer and more effective therapeutic agents for Alzheimer's disease treatment.

The study also highlights the importance of molecular docking as a reliable computational approach for predicting ligand–protein interactions during the early stages of drug discovery. However, further in vitro and in vivo studies are required to validate the biological activity, safety, and therapeutic efficacy of Huperzine A in the management of Alzheimer's disease.

CONCLUSION

The present study focused on the molecular docking evaluation of the phytochemical Huperzine A against the acetylcholinesterase (AChE) target protein associated with Alzheimer's disease to explore its potential inhibitory activity. Molecular docking is an important computational approach used in modern drug discovery for predicting the binding interaction between a ligand and a target protein.

In the current study, Huperzine A demonstrated favorable binding affinity toward the active site of the acetylcholinesterase protein, indicating the formation of a stable ligand–protein complex. The docking analysis revealed that the ligand was effectively accommodated within the binding pocket of the receptor protein and established significant intermolecular interactions that contributed to complex stabilization.

The interaction analysis showed the involvement of important amino acid residues through hydrogen bonding and hydrophobic interactions. These molecular interactions play a vital role in stabilizing the docked complex and enhancing the inhibitory potential of Huperzine A against the acetylcholinesterase target protein.

The binding affinity obtained during the docking study suggested that Huperzine A possesses good interaction capability with the active site region of the acetylcholinesterase enzyme. The 2D and 3D visualization studies further confirmed the proper orientation and effective binding mode of Huperzine A within the receptor cavity.

Such interactions indicate that Huperzine A may inhibit the activity of acetylcholinesterase, thereby increasing acetylcholine levels in the brain and improving cholinergic neurotransmission, which is essential in the management of Alzheimer's disease.

Alzheimer's disease remains one of the most serious neurodegenerative disorders worldwide, and the increasing prevalence of cognitive impairment has created an urgent need for the discovery of safer and more effective therapeutic agents. Natural phytochemicals have gained considerable importance in pharmaceutical research due to their therapeutic potential, structural diversity, neuroprotective properties, and reduced toxicity compared to synthetic compounds.Therefore, the present molecular docking study suggests that Huperzine A possesses promising acetylcholinesterase inhibitory potential and may serve as a potential lead molecule for the development of anti-Alzheimer therapeutic agents. However, further in vitro and in vivo studies are required to validate its biological activity, safety, and clinical efficacy in the tretment of Alzheimer's disease.

RESULT & DISCUSSION

SR. NO	PARAMETER	RESULT
1.	Ligand Name	Huperzine A
2.	Target Protein	Acetylcholinesterase (AchE)
3.	PDB ID	4EY7
4.	Docking Software	Auto dock vina/Pyrx
5.	Binding Affinity	-9.7 kcal/mol
6.	Important Amino Acid Interactions	TRP A:86 TYR A:337 TYR A:341 PHE A:338
7.	Interaction Types	Hydrogen bonding, hydrophobic interaction, Van der Waals interaction
8.	Binding Site	Catalytic active site
9.	Interpretation	Strong binding affinity and stable interaction

10.	RMSD Value	Within acceptable docking range (0)
11.	Hydrogen Bonding	Weak hydrogen bonding
12.	2D Ligand Interaction Analysis	2D interaction map showed hydrophobic contacts between Huperzine A and active site residues
13.	3D Ligand Interaction Analysis	Stable binding orientation of Huperzine A observed inside the active binding pocket of AchE protein

The docked ligand showed significant interactions with amino acid residues TRP A:86, TYR A:337, TYR A:341, and PHE A:338 through π–π stacked and π–π T-shaped interactions, while SER A:203, GLY A:121, TYR A:124, ASP A:74, and GLY A:448 contributed via van der Waals interactions."

The docking results demonstrated that Huperzine A possesses strong binding affinity toward acetylcholinesterase with a docking score of -9.4 kcal/mol. Lower binding energy values indicate greater stability of the protein–ligand complex. Huperzine A interacted with important catalytic and peripheral active site residues including Ser203, Trp86, Tyr337, and His447. These amino acid residues play a significant role in substrate recognition and catalytic activity of acetylcholinesterase.

Hydrogen bond formation with Ser203 contributed to stabilization of the ligand within the catalytic pocket, while hydrophobic interactions with Trp86 and Tyr337 enhanced binding strength. The interaction pattern suggests that Huperzine A can effectively block the active site of acetylcholinesterase, thereby preventing hydrolysis of acetylcholine and increasing neurotransmitter concentration in the synaptic cleft. This mechanism may improve memory and cognitive function in Alzheimer's disease patients.The obtained docking results were comparable to standard acetylcholinesterase inhibitors reported in previous studies, indicating the potential of Huperzine A as a promising natural therapeutic agent for Alzheimer's disease management.

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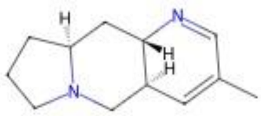
IN SILICO STUDY PARAMETERS(ADMET)

Molecule 1



SMILES CC1=C[C@@H]2[C@@H](N=C1)C[C@H]1N(C2)CCC1

Physicochemical Properties	
Formula	C12H18N2
Molecular weight	190.28 g/mol
Num. heavy atoms	14
Num. arom. heavy atoms	0
Fraction Csp3	0.75
Num. rotatable bonds	0
Num. H-bond acceptors	2
Num. H-bond donors	0
Molar Refractivity	66.80
TPSA	15.60 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	Temporarily unavailable
Log $P_{o/w}$ (XLOGP3)	Temporarily unavailable
Log $P_{o/w}$ (WLOGP)	1.11
Log $P_{o/w}$ (MLOGP)	1.84
Log $P_{o/w}$ (SILICOS-IT)	Temporarily unavailable
Consensus Log $P_{o/w}$	

Water Solubility	
Log S (ESOL)	-1.02
Solubility	1.82e+01 mg/ml ; 9.56e-02 mol/l
Class	Very soluble
Log S (Ali)	0.12
Solubility	2.52e+02 mg/ml ; 1.32e+00 mol/l
Class	Highly soluble
Log S (SILICOS-IT)	Temporarily unavailable
Solubility	mg/ml ; mol/l
Class	

Pharmacokinetics	
GI absorption	High
BBB permeant	Yes
P-gp substrate	Temporarily unavailable
CYP1A2 inhibitor	Temporarily unavailable
CYP2C19 inhibitor	Temporarily unavailable
CYP2C9 inhibitor	Temporarily unavailable
CYP2D6 inhibitor	Temporarily unavailable
CYP3A4 inhibitor	Temporarily unavailable
Log K_p (skin permeation)	-7.46 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: MW<200
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: MW<250
Synthetic accessibility	4.40

The ADMET prediction results indicated that Huperzine A possesses favourable pharmacokinetic properties suitable for central nervous system drug development. The compound exhibited high gastrointestinal absorption, suggesting efficient oral uptake after administration. Blood–brain barrier permeation prediction was positive, which is an important characteristic for anti-Alzheimer drugs because therapeutic agents must reach brain tissue to exert pharmacological effects.

Huperzine A successfully satisfied Lipinski's Rule of Five, indicating good drug-likeness and oral bioavailability. The moderate Log P value suggested balanced hydrophilic and lipophilic properties, which are essential for membrane permeability and absorption. The compound also showed low CYP450 inhibition potential, indicating a lower probability of adverse drug–drug interactions during metabolism.

The toxicity prediction revealed low toxicity and acceptable safety characteristics. Furthermore, the absence of P-glycoprotein substrate behavior suggested reduced drug efflux from brain cells, thereby enhancing central nervous system availability. Overall, the ADMET profile supported the therapeutic potential of Huperzine A as an effective acetylcholinesterase inhibitor for Alzheimer's disease treatment.

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