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Molecular Docking, In-Silico Screening of *Spermacoce Latifolia* and *Celastrus Paniculatus* as Ache and Buche Inhibitors for Neurodegenerative Diseases

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KEYWORDS

in-silico docking, AutoDock vina tool, Alzheimer's disease, acetylcholinesterase, butyrylcholinesterase, *Spermacoce latifolia* and *Celastrus paniculatus*.

ABSTRACT:

Objective: To perform in-silico docking studies of AChE and BuChE inhibitors from *Spermacoce latifolia* and *Celastrus paniculatus* for neurodegenerative diseases.

Methods: In the present study, molecular docking stimulation were conducted using the AutoDock vina tool to asses the binding interactions of naturally occurring compounds from *Spermacoce latifolia* and *Celastrus paniculatus* with acetylcholinesterase and butyrylcholinesterase, enzymes of significant importance within the central nervous system (CNS).

Results: AChE and BuChE inhibitor , AChE and BuChE involved hydrogen bonding, Van der Waals forces and Pi-sigma/Pi-Pi interactions primarily mediated by Fluorophore Thioflavin T.

Conclusion: Molecular Dynamics Stimulations (MDS) supported the stability of these interactions. AChE and BuChE were hydrolytic enzymes that degrade the Acetylcholine (Ach), terminating synaptic transmission. Despite their abundance in the healthy brain they minimally regulate brain ACh levels. In Alzheimer's, BuChE activity raises while AChE activity remains stable or falls. Both enzymes were potential therapeutic targets to address the cholinergic defect associated with cognitive, functional and behavioral decline. This plant, used medicinally locally is rich in flavonoids including ascorbic acid, epicatechin, apigenin, luteolin, rutin, tangeritin, hesperetin, taxifolin and eriodictyol. Therefore, These results clearly revealed that the bioactive compound *Spermacoce latifolia* and *Celastrus paniculatus* have good binding interactions when compared to the standard drugs.

1. Introduction

Memory disorder like Alzheimer's is characterized by a persistent and irreversible decline in cognitive function caused by senile plaques in the hippocampus of the brain. AD is the most frequent type of dementia among middle-aged and older adults, affecting more than 6 million Americans and by 2050 it is predicted to reach 14 million. Alzheimer's disease is a neurodegenerative disorder. Alzheimer's disease is characterised by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions, including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus. It is the cause of 60-70% of cases of dementia. About 70% of the risk is believed to be inherited from a person's parents with many genes usually involved. Acetylcholinesterase is the primary cholinesterase in the body. It is an enzyme that catalyses the breakdown of acetylcholine and some of other choline esters that functions as neurotransmitters. AChE is found mainly at neuromuscular junctions and in chemical synapses of cholinergic type, where its activity serves to terminate synaptic transmission. This termination of actions in the synaptic cleft leads to etiology of Alzheimer's disease. Butyrylcholinesterase (BchE) is a nonspecific cholinesterase enzyme that

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hydrolyses many different choline-based esters. Acetylcholinesterase (AChE) terminates synaptic transmission at cholinergic synapses by rapid hydrolysis of the neurotransmitter acetylcholine (ACh). It has become an important drug target because partial inhibition of AChE results in modest increases in ACh levels that can have therapeutic benefits; thus, AChE inhibitors that penetrate the blood-brain barrier have proved useful in the symptomatic treatment of Alzheimer's disease. Molecular docking is a key tool in structural molecular biology and computer-assisted drug design. The goal of ligand-protein docking is to predict the predominant binding mode of a ligand with a protein of known three-dimensional structure.

2. Objectives

To perform in-silico docking studies of AChE and BuChE inhibitors from *Spermacoce latifolia* and *Celastrus paniculatus* for neurodegenerative diseases.

3. Methods

Protein preparation:

The crystal structure of acetylcholinesterase and butyrylcholinesterase bound to Protein (PDB ID: 2J3Q & 4BDS) was retrieved from the Protein Data Bank at a resolution of 2.0 Å. The enzyme was refined using the Protein Preparation Wizard, which comprises two primary steps: preparation and refinement. The algorithm within the wizard addresses terminal capping, adds missing hydrogens and residues, and assigns bond orders. Energy minimization was performed using the OPLS force field. Water molecules were removed from the vicinity of the active site. Disulfide bonds were built, and Prime was employed to fill in gaps in the protein chain and model loops extending beyond 5 Å.

Ligand Preparation:

Ligands were prepared using AutoDock Vina. The OPLS 2005 force field was employed, and ionization states were determined using the EPIK application. Desalting was performed to identify potential tautomers. Customized chiralities were defined for the ligands, and the process was executed to generate low-energy ring conformations.

Molecular docking:

Ligand docking and binding affinity prediction were performed using Autodock Vina. Receptor and ligand structures in PDBQT format were input, and the software was executed. Cluster analysis based on RMSD values relative to the starting geometry was conducted, and the lowest energy conformation of the most populated cluster was selected as the most reliable solution. Binding affinities for three protein targets were calculated and used to classify compounds. To assess in silico performance, molecular interactions between receptors and compounds with binding affinities equal to or greater than standard inhibitors were visualized.

Selection, modelling, and drug-likeness test of phytochemicals for drug design

(i) Selection of phytochemicals from medicinal plants for inhibitor design

The medicinal plant was selected for the identification of phytochemicals based on their inhibitory property against acetylcholinestrease. The medicinal plants for the studies: *Spermacoce latifolia* and *Celastrus paniculatus*. Phytochemicals from above said plants (possessing cognitive function, neuroprotective, antiinflammation, digestive issues and antioxidant effects) were retrieved from extensive literature survey for ligand (inhibitor) preparation to act against acetylcholinesterase. Their respective two-dimensional chemical structures in structured data format (SDF) were retrieved from PubChem-NCBI database and SDF format was converted into Protein data bank (PDB) format.

(ii) Drug-likeness test of phytochemicals based on the Lipinski rule

To perform docking studies, the phytochemicals retrieved from medicinal plant should satisfy drug-likeness test (determines whether particular compound could be used as the drug). The evaluation of drug-likeness test for all compounds was carried out. This tool evaluates the compounds based on the Lipinski rule, which states that an active oral drug should qualify the following criteria: molecular weight should be in the range from 130 to 725 Da, log P should be < 5, H-bond donor should be 0- 6, H-bond acceptor should be 2-20, number of rotatable bonds should be > 5. Along with drug-likeness test, molecular volume for the compounds should be between 500 and 2000.

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(iii) Development of phytochemical models for docking

The predicted Lipinski values (data sets) of compounds for acetylcholinestrease were used for the development of the phytochemical models. The result analysis studies were carried out to correlate datasets—descriptors of plant compounds along with Fluorophore Thioflavin T for acetylcholinestrease. The descriptors of compounds (log P, molecular weight, H-bond donor, H-bond acceptor, number of rotatable bonds, molecular volume) were compared manually with the standard values in addition to volume. The phytochemicals which exhibit maximums number of properties within the range of standard values were selected for further docking studies with 3D structure of representative acetylcholinestrease.

Docking studies using AutoDock Vina

(i) Preparation of modelled acetylcholinestrease and ligands for docking

The representative homology model of acetylcholinestrease molecule from Swiss model server did not have a complete charge assigned to them. Hence, before docking, polar hydrogens were added to the macromolecules and then assigned the partial atomic charges using Auto Dock Vina. The non-polar and polar hydrogen atoms were merged. For ligands along with conventional drugs for comparison, Gasteiger charges were added, non-polar hydrogens were merged and also rotatable bonds were determined based on the nature of ligand molecule. TORSDOF was used to calculate the change in free energy (δG) caused by the loss of torsional degree of freedom upon binding. The atomic fragmental volume and the atomic solvation parameters were used here to calculate the energy contribution of the desolvation of the macromolecules by ligand binding. Peptide backbone bonds were constructed. Bonds between selected atoms and all the active bonds are made rotatable. Grid maps were generated and spacing was adjusted to 0.8 Å to enable ligand binding. The grid dimension was adjusted to 40 × 40 × 40 points. Auto Dock Vina uses interaction maps for docking. Prior to the actual docking run, these maps were calculated by Auto Grid. For each ligand atom type, the interaction energy between the ligand atom and receptor was calculated for the entire binding site, which is discretized through a grid. The protein was embedded in a 3D grid and a probe was placed at each grid point. The interaction energy of the protein was assigned at each grid point and the affinity for each of the ligand was calculated.

(ii) Docking protein and ligand molecules

Automated docking software Auto Dock Vina was used to evaluate binding affinity of ligands (with drug-likeness property) to homology model of acetylcholinestrease. Docking energy of all ligand molecules and drugs were evaluated by using empirical-free energy functions and Lamarckian genetic algorithm. These tools calculate binding-free energy (δG) based on different electrostatic, Vander Waal, hydrogen bonding, and desolvation effects. Docking precision was set to “regular precision” and “flexible” ligand-docking mode was employed for each docking run. The stability of each docked pose was evaluated using Auto dock energy calculations.

Drug Name	Molecular Weight	LogP	H Bond Donors	H Bond Acceptors
Urosolic acid	456.711	7.0895	2	2
Stigmasterol	412.702	7.8008	1	1
Iridiods	456.4	-2.7674	5	12
Beta sitosterol	414.718	8.0248	1	1
Celastrine	572.698	6.1722	0	7
Celapanine	569.607	3.9026	0	11
Paniculatin	594.522	-2.3934	11	15
Lupeol	426.729	8.0248	1	1

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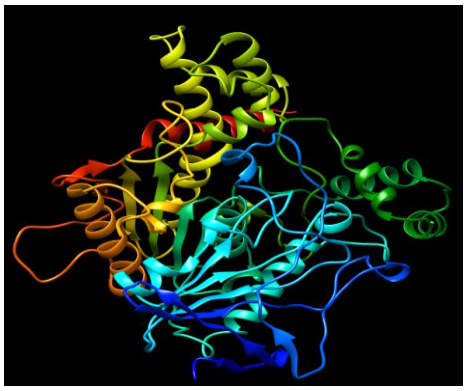
4. Results

In-silico Molecular Docking Studies for AChE inhibition



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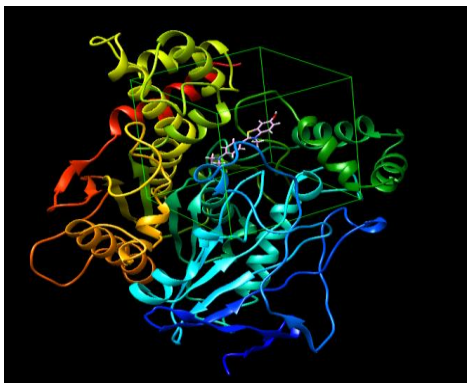

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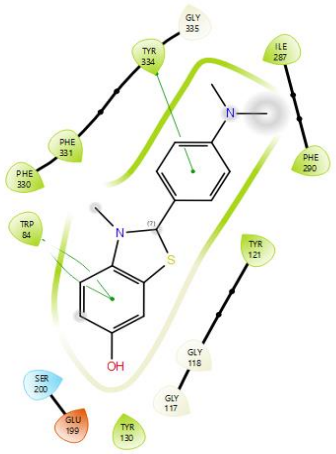
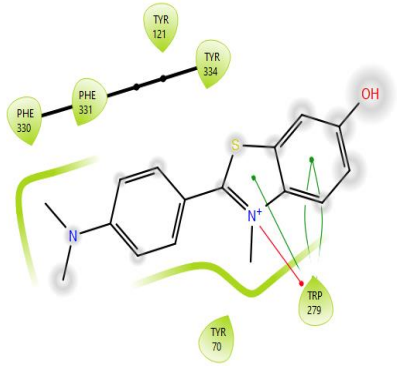


(c)

Fig.1 The structure (a) surface model of protein (b) binding site (c) The best-docked pose formed by Tacrine protein with AChE

Fig.2 The best surface model of Beta sitosterol.



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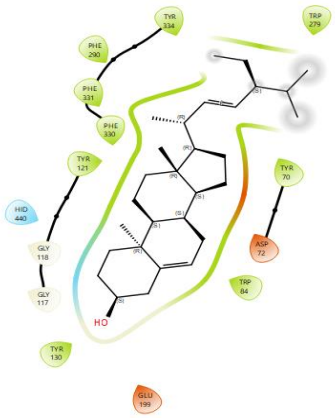

(b)

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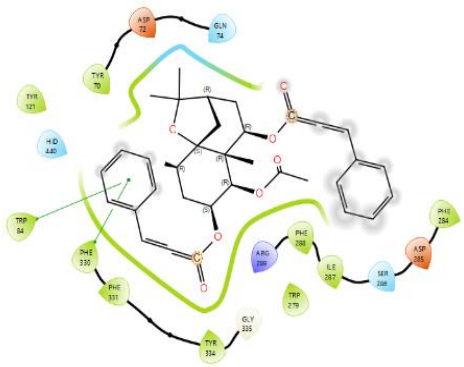
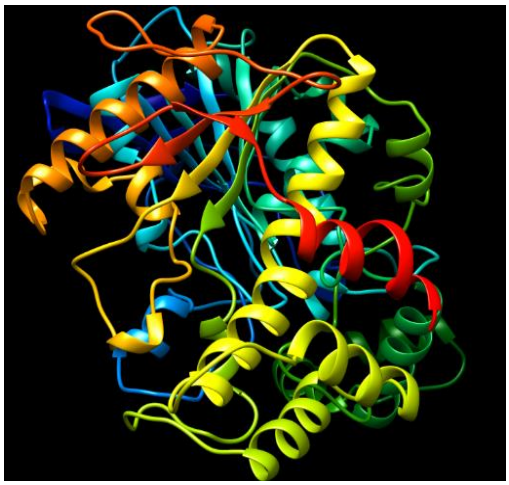


(c)

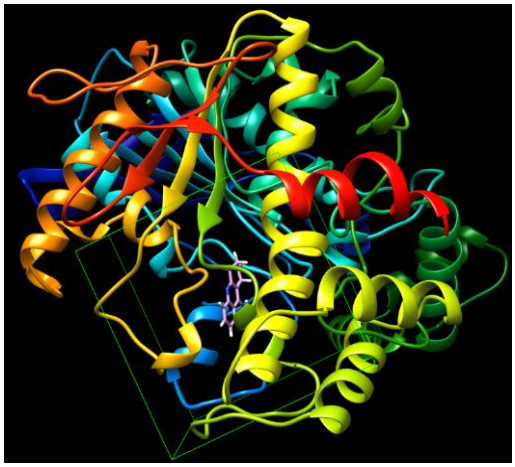
Fig.3 The best-docked pose of bioactive compounds from *Spermacoce latifolia* and *Celastrus paniculatus* (a))Beta sitosterol, (b Stigmasterol and (c) Celastrine with Tacrine protein

Ligands	Docking scores
Beta sitosterol	-12.1
Celapanine	-7.7
Celastrine	-11
Iridiods	-10.2
Lupeol	-10.9
Paniculatin	-8.6
Stigmasterol	-11.3
Urosoli acid	-10.5
Reflig prepared (Tacrine)	-8.7

In-silico Molecular Docking Studies for BuChE inhibition



(a)



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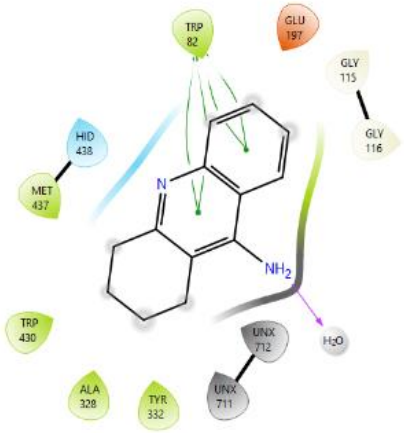

(c)

Fig.4 The structure (a) surface model of protein (b) binding site (c) The best-docked pose formed by Tacrine protein with BuChE.

Fig.5 The best surface model of Celastrine

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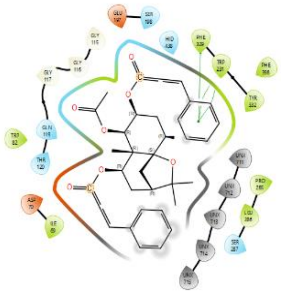
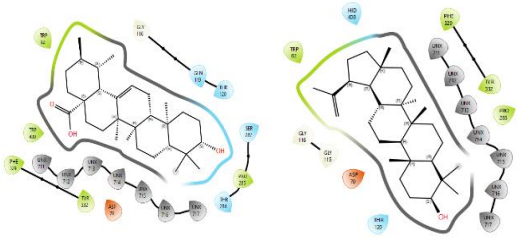


(a)



(b) (c)

Fig.6 The best-docked pose of bioactive compounds from *Spermacoce latifolia* and *Celastrus paniculatus* (a)) Celastrine, (b Urosolic acid and (c) Lupeol with Tacrine protein

Ligands	Docking scores
Beta sitosterol	-9.3
Celapanine	-10.3
Celastrine	-11.6
Iridiods	-9.5
Lupeol	-10.4
Paniculatin	-9.5
Stigmasterol	-10
Urosolic acid	-11.4
Dock reflig.ligand (Tacrine)	-8.1

Discussion

Since we knew that the AchE and BuchE are the bio markers for the neurodegenerative diseases like Alzheimer's disease. All the selected active constituents from the plants spermacoce latifolia and Celastrus paniculatus has showed the better docking score with targeted markers of neurodegenerative diseases. From the study, it is clearly understood that all the selected active constituents has anti Alzheimer's activity by inhibiting the targeted enzymes like AchE and BuchE in in-silico. Further research studies like invitro and invivo are still needed to prove biologically that the selected active constituents are inhibitors of AchE and BuchE.

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