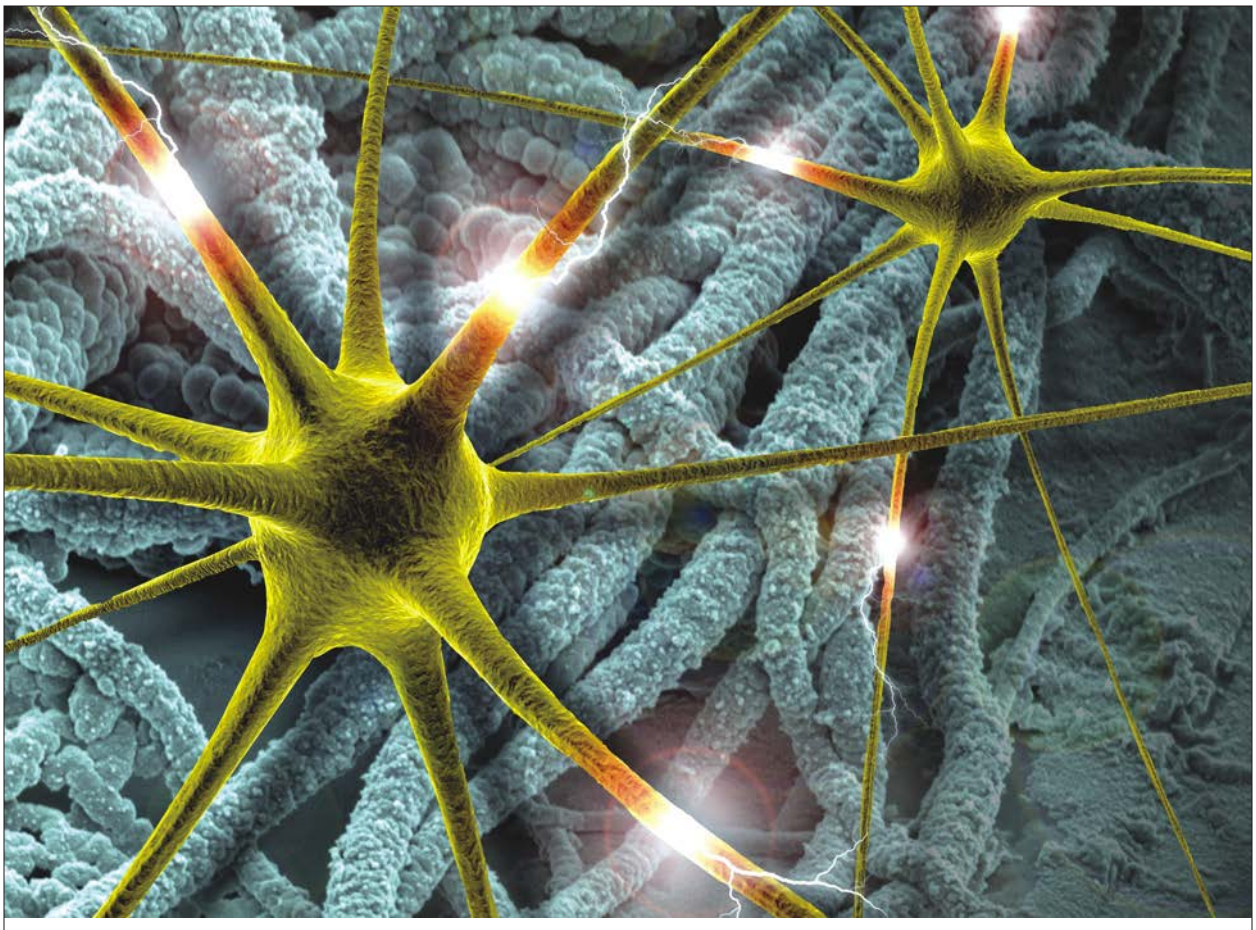

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In silico Docking of Mangrove Derived Ligands against Alzheimer's Receptor Proteins

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ABSTRACT

Docking is one of the important computational tools for identifying the structural modeling and predicting the activity of potential drug. The β-Amyloid (Aβ) and acetylcholine (AChE) are playing a role in the neurotoxicity associated with Alzheimer's disease. In the present study, five mangroves derived compounds such as avicenol A, betulinic acid, lupeol, quercetin and triterpenoid were selected for docking with target Aβ and ACHE. Lamarckian genetic algorithm methodology was employed for docking. The important parameters like binding energy, length of a hydrogen bond, amino acid residues, cluster and reference RMSD were determined. Betulinic acid and triterpenoid showed higher binding energy (-5.54 and -46.79 kcal mol^{-1}) on Aβ and AChE esterase receptor than compared to other derivatives.

Key words: Acetylcholine, betulinic acid, hydrogen bond, *in silico*

INTRODUCTION

Alzheimer's disease is one of the neurogenerative diseases, which mainly cause dementia leads to severe loss of intellectual memories. According to world Alzheimer report published at 2010, 35.6 million people living with dementia it will be increased to 65.7 million by 2030 (Wimo and Prince, 2010). The characteristic loss of AD is sequence by progressive thrashing of neurons, gathering of amyloid beta peptide, neurofibrillary tangles and hyperphosphorylated tau protein (Selkoe, 1993). Amyloid plaques are defined as clumps of amyloid beta (Aβ) which originates from proteolytic cleavage of Amyloid Precursor Protein (APP) by membrane associated β and γ secretase. It generates various peptides of different size and 1 out of them Aβ40 (1-40 amino acids) and Aβ42 (1-42 amino acids) are the most abundant ones (Bayer *et al*., 2001). Four kg Dol^{-1} of Aβ protein is the main component of amyloid plaque deposit and accumulation of abnormally folded Aβ proteins in the brain is the main causes of Alzheimer (Glenner and Wong, 1984). Most commonly used cholinesterase inhibitors are donepezil, rivastigmine and galantamine (Ritchie *et al*., 2009). Those inhibitors prevent the functioning of acetylcholinesterase which leads to increases in the level of acetylcholine and its communication between the nerve cells only temporarily stabilize the symptoms of AD. Currently available nonsteroidal anti-inflammatory drugs naproxen and ibuprofen also used to control amlyoid beta aggregation in the brain are a hallmark of Alzheimer's disease and its related disorders (Gaurav *et al*., 2014). The different mechanism of action has been

proposed to explain the physiological and pathological relationship between proteins and AD. But the available pharmaceutical drugs are not sufficient to address the problem of AD in molecular level are unknown which leads the researchers to look for cost effective drug compounds from plants. The mangroves are woody plant or a shrub that grows in tropical, subtropical, estuaries, back waters, rivers. Commonly found in the Asian countries, islands of the Indian Ocean, Arabian Sea, Bay of Bengal, South China and the Pacific (Qasim, l998). It contains an array of primary and secondary metabolites such as alkaloids, flavonoids, terpenes, pheromones, tannins have toxicological, pharmacological and ecological importance (Bandaranayake, 2002). Among the computational tools, docking is the most commonly employed techniques for calculating binding affinities and predicting binding sites (Bajorath, 2002). Number of compounds reported from mangroves plants and evaluated its therapeutic potential on diabetes, inflammation using *in silico* approachees (Gurudeeban *et al*., 2012, 2013). Therefore in the present study, molecular docking has been used for study the binding affinity of avicenol A, betulinic acid, lupeol, quercetin and triterpenoid to amyloid peptide (Aβ1-42) and acetylcholine esterase then only the possibility of using these ligand molecules in treating Alzheimer's (AD) can be explored.

MATERIALS AND METHODS

Preparation of receptor molecules: The β amyloid peptide (Aβ) and acetylcholine esterase (AChE) 3D crystal structure was downloaded from the PDB structural database site. PDB ID of the receptor proteins was 1IYT and 1B41 used as a docking target.

Ligand preparation: The 2D structure of mangrove derived ligands viz., avicenol A, betulinic acid, lupeol, quercetin and triterpenoid were retrieved from PubChem database (Table 1). Optimized ligand molecules were docked into distinguished model using Lig and Fit theory.

Identification of the amyloidogenic regions: An amyloidogenic region in polypeptide chains is very important because such regions are responsible for amyloid formation and aggregation. Amyloidogenic region of the protein was predicted using web server Fold Amyloid, which predicts the specific sequence(s) on a polypeptide chain which is likely to form aggregates based on the physicochemical properties of the amino acid residues.

Docking methodology: AutoDock Tools 4.0 was used to prepare, run and analyze the docking simulations. The pre calculated grid maps, one for eAChE atom type present in the flexible molecules being docked and its stores the potential energy arising from the interaction with rigid macromolecules. The Lamarckian Genetic Algorithm (LGA) 23 was chosen search for the best conformers. AutoDock results were analyzed to study the interactions and the binding energy of the docked structure. All the Auto Dock docking runs were performed in Intel Centrino, 32 bit Operating System and 1 GB RAM in HP Pavilion dv6000.

Table 1: List of ligand used for docking

Compound	PubChem ID	Hydrogen donor/acceptor	Molecular weight
Avicenol A	11208912	(2, 5)	-8.06
Betulinic acid	64971	(2, 3)	456.70
Lupeol	259846	(1, 1)	426.72
Quercetin	5280343	(5, 7)	302.24
Triterpenoid	9804218	(2, 3)	458.60

RESULTS

The structure of protein is viewed by PyMol and predicted active sites of Aβ and AChE have delH-2.051e-03 and 1-954e-02, respectively. The docking poses were ranked according to their docking scores and both the ranked list of docked ligands and their corresponding binding poses (Zhang *et al*., 2008). The 10 docking runs were performed. Grid parameters were set as mentioned earlier and spacing between grid points were 0.375 Å. After the simulations were complete, the docked structures were analyzed and the interactions were observed. Hydrogen bond interactions and binding distance between the donors and acceptors were measured for the best conformers. Distinct conformation clusters RMSD-tolerance and Van der Waals scaling factor was found to be 2.0 and 1.0 Å, respectively.

The mangrove derived bioactive molecules such as avicenol, betulinic acid, lupeol, quercetin, triterpenoid and its binding energy, hydrogen bond interactions distance between hydrogen donor and acceptor atoms of Aβ ligand is presented in Fig. 1. After successful docking of five ligand molecules from mangroves on acetylcholine esterase receptor based on the parameters such as hydrogen bond, binding energy, cluster and reference RMSD were shown in Fig. 2. Among these,

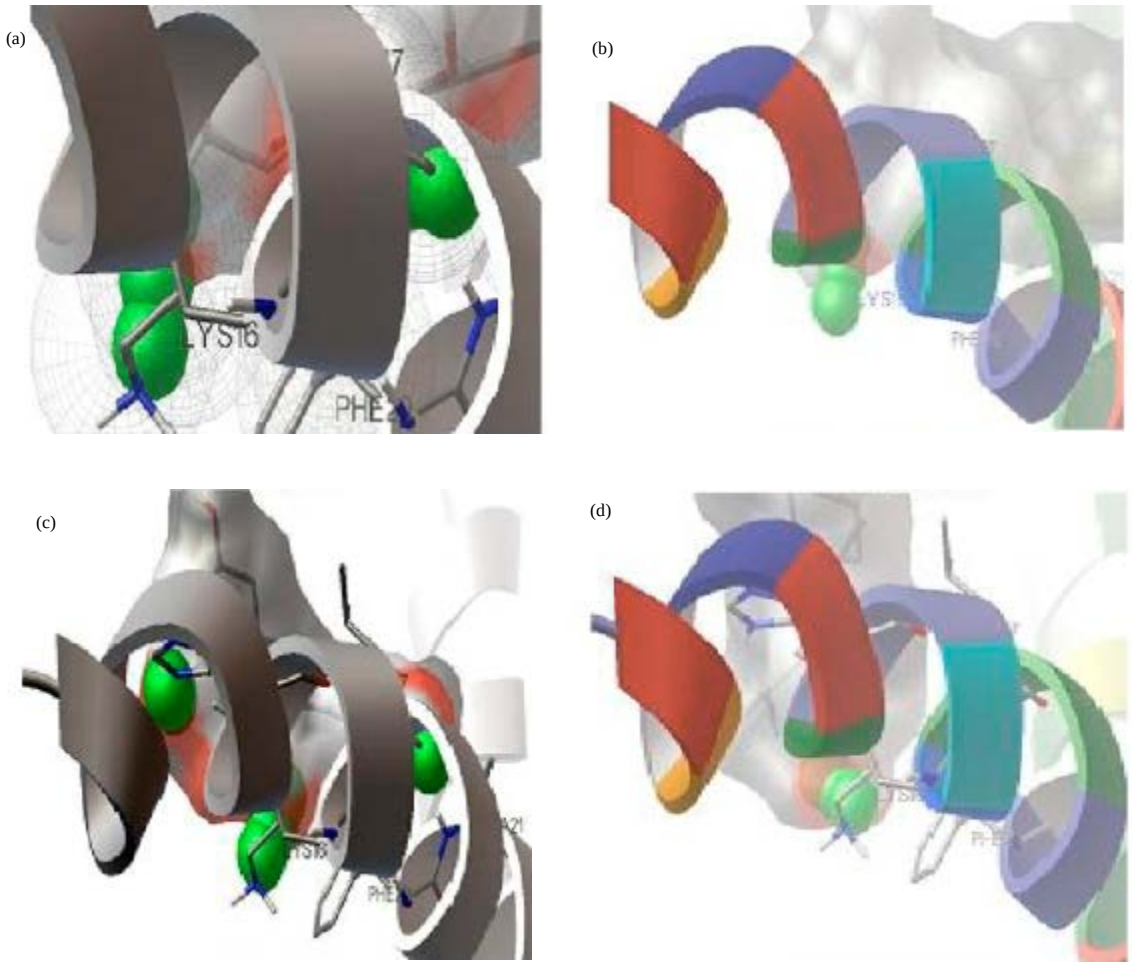

Fig. 1(a-d): Molecular interaction of β-Amyloid (A) receptor with mangrove derived ligands, (a) Avicenol A, (b) Betulinic acid, (c) Quercetin and (d) Triterpenoid

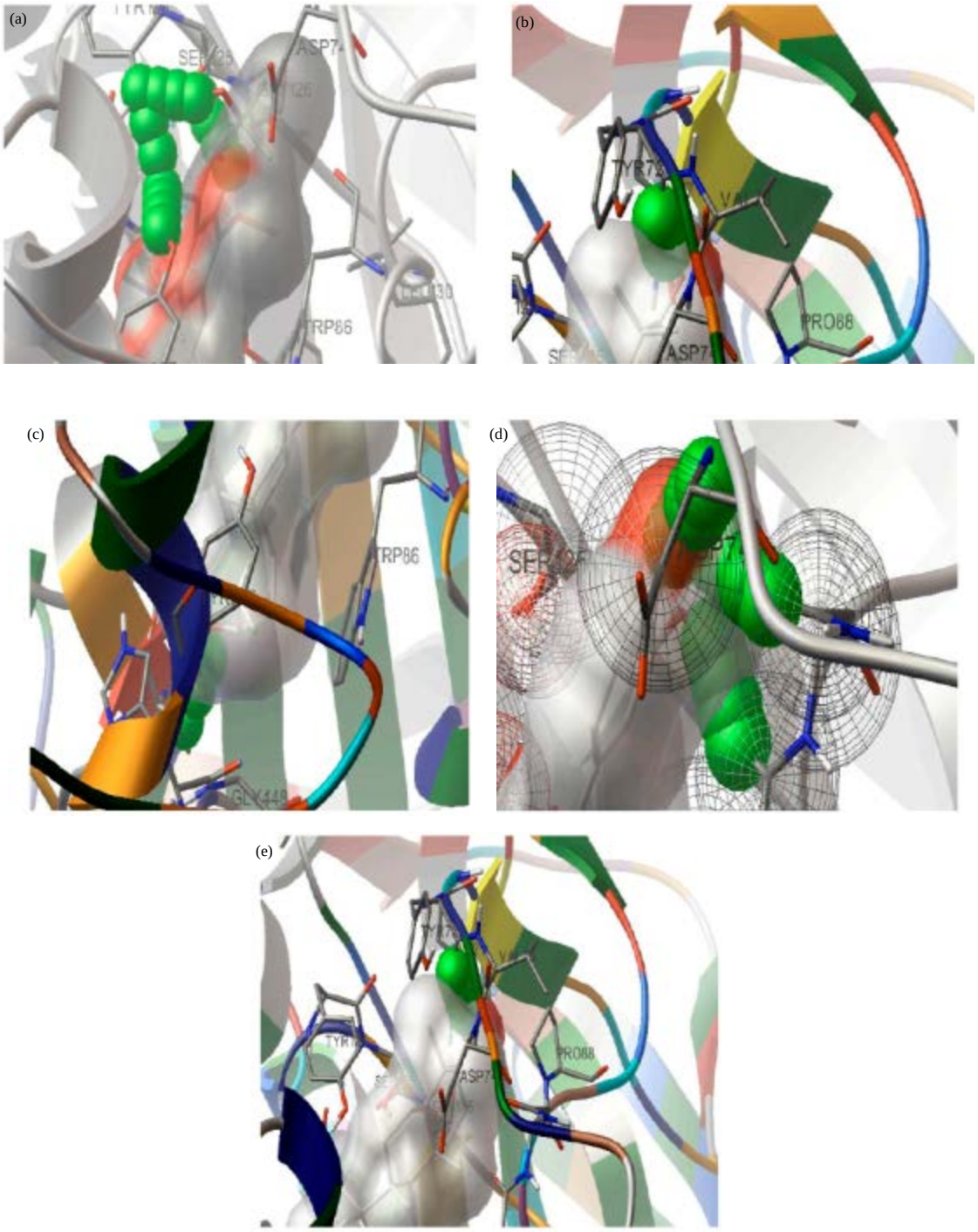

Fig. 2(a-e): Molecular interaction of acetylcholine esterase receptor with mangrove derived ligands, (a) Avicenol A, (b) Betulinic acid, (c) Lupeol, (d) Quercetin and (e) Triterpenoid

Table 2: Molecular interactions of phyto compounds on β-Amyloid (Aβ) receptor

Ligand	No. of H-bonds	Binding energy	Length of hydrogen bond (A)	Cluster RMSD	Reference RMSD
Avicenol A	2	-4.25	2.677	1.39	3.95
			2.141		
Betulinic acid	1	-5.54	1-923	0.35	4.47
Lupeol			No interaction		
Quercetin	3	-4.31	1.953	0.00	3.30
			1.667		
			1.908		
Triterpenoid	1	-4.37	1.733	1.47	4.46

Table 3: Molecular interactions of phyto compounds on acetylcholine esterase receptor

Ligand	No. of H-bonds	Binding energy	Length of hydrogen bond (A)	Cluster RMSD	Reference RMSD
Avicenol A	4	-7.26	1.898	0.00	209.56
			1.764		
			2.032		
			1.973		
Betulinic acid	1	-37.74	1.273	0.49	207.87
Lupeol	1	-27.01	2.012	0.71	207.91
Quercetin	4	-8.18	2.017	0.00	208.70
			1.942		
			1.785		
			2.035		
Triterpenoid	2	-46.79	2.205	0.29	207.20
			1.208		

betulinic acid had significant binding energy -5.54 kcal mol^{-1} and interacted with receptor protein in LYS16 amino acid residue (Table 2). Among molecular interactions of five mangroves on acetylcholine esterase receptor, the triterpenoid had significant binding energy -46.79 kcal mol^{-1} and the compounds interacted with receptor protein in TYR 72 amino acid residue (Table 3).

DISCUSSION

The discovery of plant metabolites for AD is an increasingly important task for early diagnosis and for use in experimental medicine. In the present study the avicenol A, betulinic acid, lupeol, quercetin and triterpenoid to amyloid peptide (Aβ1-42) and acetylcholine esterase are considered to be safe, thus have potential for developing effective therapeutic molecules for neurological disorders, such as AD. Earlier reports showed the various mangrove derived metabolites, including alkaloids reported for their anti-cholinergic action through docking with acetyl cholinesterase (AChE) as target (Naaz *et al.*, 2013).

Crescenzi *et al.* (2002) pointed the short Aβ peptide contains 1 to 42 residues and its structure showed two alpha helical regions which are joined by regular type I beta turn. First and second helical region encompassing 8-25 and 28-38 residues. Mangrove plant *Avicennia marina* is a promising source of betulinic acid is a triterpenoids and used for the treatment of different bacterial infections (Hingkua *et al.*, 2013). Pharmacologically, betulinic acid is being administered for a variety of human pathologies including cancer, nervous disorders and HIV (Kashiwada *et al.*, 1996). In the present study, betulinic acid from mangrove plants indicates significant docking results on Aβ protein which involved in prevention of Alzheimer's diseases.

Planchard *et al.* (2012) explored the *in vitro* interactions between a betulinic acid natural product and Aβ42 peptide. Also it has the unique property of promoting Aβ fibril formation and especially bypassing or accelerating the clearance of toxic oligomers along the fibril formation, it makes the potential of betulinic acid on AD.

Acetylcholine is a neurotransmitter hydrolyzed by acetyl cholinesterase (AChE). Earlier reports supported that the AchE inhibitors have showed better results in the treatment of AD than compared to nicotine acetylcholine receptor agonists, NMDA receptor antagonists, AMPA-receptor modulators, caspase inhibitors, antioxidants and anti-inflammatory agents (Bermudez-Lugo *et al.*, 2011; Salloway *et al.*, 2008). Among the five mangroves derived ligands on AChE, betulinic acid, triterpenoid and lupeol indicates high binding energy. It is efficiently might be used to treat AD.

CONCLUSION

In conclusion, bioactive compounds from mangroves offer an attractive alternative to synthetic drug treated for the AD. Also it might be additional benefits to human health. Furthermore clinical trials of the same are required before development of potential chemical entities for the prevention and treatment of AD.

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