ISSN: 2574-1241
DOI: 10.26717/BJSTR.2018.12.002235
Mohuya Majumder. Biomed J Sci & Tech Res

BIOMEDICAL Journal of Scientific & Technical Research

Research Article Open Access

Insilico Molecular Docking of some Isolated Selected Compounds of Lantana Camera against Alzheimer's Disease

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Received: December 10, 2018; **Published:** December 18, 2018

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Abstract

Lantana Camera (L.) (Family-Verbenaceae) is commonly known as Chotra, is found in fallow lands throughout Bangladesh. The plant has used for carminative, astringent, tonic properties and uterine infection by the tribal in Khagrachari, Bangladesh. Our aim of the study to performed molecular docking studies to identify potential binding affinities of the phytocompounds from *Lantana Camera* (L.), namely 1-hexanol and 1-octen-3-ol towards Ach and BACE1 for searching of lead molecule against Alzheimer's disease. A wide range of docking score found during molecular docking by Schrodinger. 1-hexanol and 1-octen-3-ol showed the docking score respectively -2.291kj/mol and -2.465kj/mol against Ach & -0.948kj/mol and -1.267kj/mol against BACE1. Between all the compounds 1-octen-3-ol showed best docking score towards Ach & BACE1. So, 1-octen-3-ol is the best compound for Ach and BACE1 enzyme inhibition, as it possessed best value in Molecular docking. Further *in vivo* investigation need to identify Ach & BACE1 enzyme inhibitory activity of isolated compounds from *L.Camera* (L.).

Keywords: *Lantana Camera* (L.); Ach; BACE1; Molecular docking; 1-octen-3-ol

Introduction

Alzheimer's disease (AD) is the most common cause of dementia and is a progressive neurodegenerative disorder [1,2]. It is characterized by histopathological changes, designated as senile plaques and fibrillary deposits, which ultimately lead to the death of neuronal cells in the cerebral cortex of the brain [3-5]. Alzheimer's disease is the most frequent cause of dementia in Western societies. In the US, approximately 5.5 million people are affected, and the prevalence worldwide is estimated to be as high as 24 million. In both established and developing nations are rapidly aging, the frequency is expected to double every 20 years until 2040 [6,7]. The familial form of AD is rare, affecting less than five percent of AD patients and has been associated with mutations of Presenilin 1 (PSEN1), Presenilin 2 (PSEN2) and Amyloid Precursor Protein (APP) [8]. These mutations result in incorrect cleavage of the protein, producing a deposited protein of amyloid-β (Aβ) that is more likely to form plaques [5,9].

Alzheimer's disease is characterized by progressive dementia beginning in middle to late life, with death occurring an average

of 8-10 years after diagnosis. The greatest known risk factor for Alzheimer's is increasing age. Most individuals with the disease are 65 and older. Another risk factor is family history. Research has shown that those who have a parent, brother or sister with Alzheimer's are more likely to develop the disease than individuals who do not. The clinical manifestations of the disease are extremely variable, with symptoms including memory loss, confusion, personality changes, impaired coordination and speech problems [2,10-12].

Lantana camara Linn. (Family: Verbenaceae) is a pantropical weed, affecting pastures, orchards and native forests in about 70 countries worldwide [13]. It also known as Chotra (Bengali) [14]. Folk healers in Asia and South America have used lantana species including *Lantana camara* for centuries to treat various human ailments such as dermatological and gastrointestinal diseases, tetanus, malaria and tumors [15]. Traditional healers have used lantana species for centuries to treat various diseases. Different parts of *L. camara* is used for the treatment of various human ailments such as itches, cuts, ulcers, swellings, bilious fever, catarrh, eczema, tetanus, malaria, tumors and rheumatism [16,17].

A productive docking strategy must have the ability to adequately envision the local ligand represent the receptor limiting site (i.e.to find the trial ligand geometry inside a resistance confine) and the related physical-compound sub molecular affiliations [18-20]. The aim of this study was to screen out the effective bioactive compounds from *Lantana camara* Linn., which may be potential inhibitors of Alzheimer's disease in future and may act as a drug which may be effective in preventing the Alzheimer's disease.

Materials and Methods

In silico Molecular Docking Protein Preparation

Three-dimensional crystal structure of Ach (PDB id: 2CKM) and BACE1 (PDB id: 4IVT) was downloaded in pdb format from the protein data bank [21]. After that, structure was prepared and refined using the Protein Preparation Wizard of Schrödinger-Maestro v10.1. Charges and bond orders were assigned, hydrogens were added to the heavy atoms, selenomethionines were converted to methionines and all waters were deleted. Using force field OPLS_2005, minimization was carried out setting maximum heavy atom RMSD (root-mean-square-deviation) to 0.30Å.

Ligand Preparation

Compounds were retrieved from Pubchem databases, i.e. 1-hexanol and 1-octen-3-ol. The 3D structures for these were built by using Lig prep 2.5 in Schrödinger Suite 2015 with an OPLS_2005 force field. Their ionization states were generated at pH 7.0±2.0 using Epik 2.2 in Schrödinger Suite. Up to 32 possible stereoisomers per ligand were retained.

Receptor grid generation

Receptor grids were calculated for prepared proteins such that various ligand poses bind within the predicted active site during docking. In Glide, grids were generated keeping the default parameters of van der Waals scaling factor 1.00 and charge cutoff 0.25 subjected to OPLS 2005 force field. A cubic box of specific dimensions centered around the centroid of the active site residues (Reference ligand active site) was generated for receptor. The bounding box was set to 14 Å × 14 Å × 14 Å for docking experiments.

Glide Standard Precision (SP) ligand docking

SP flexible ligand docking was carried out in Glide of Schrödinger-Maestro v 10.1 [22,23]. within which penalties were applied to non-cis/trans amide bonds. Van der Waals scaling factor and partial charge cutoff was selected to be 0.80 and 0.15, respectively for ligand atoms. Final scoring was performed on energy-minimized poses and displayed as Glide score. The best docked pose with lowest Glide score value was recorded for each ligand.

Results

In silico Molecular docking Analysis

Advances in computational techniques have enabled virtual screening to have a positive impact on the discovery process. Virtual screening utilizes docking and scoring of each compound from a dataset and the technique used is based on predicting the binding modes and binding affinities of each compound in the dataset by means of docking to an X-ray crystallographic structure [24]. Grid based docking study was used to analyze the binding modes of molecules with the amino acids present in the active pocket of the protein [25]. To identify the potential novel compound lead molecule, we have subjected the docking analysis of the active compounds of *L. camara* (L.) to the active site of BACE1. In order to study the interaction of the compounds 1-hexanol and 1-octen-3-ol with Ach (2CKM) and BACE1 (PDB id: 4IVT). We performed Glide docking analysis by Schrodinger suite v10.1, where among of these compounds 1-octen-3-ol shows highest docking score against both enzymes. Docking Score suggested that 1-octen-3-ol had the highest affinity to the Ach and BACE1 corresponding to the other compound. The results of docking analysis were described in Tables 1 & 2 and the docking figure showed in Figure 1.

Table 1: Docking results of 1-hexanol and 1-octen-3-ol with Ach (PDB id: 2CKM).

Compound name	Compound ID	Docking score	Glide emodel	Glide energy
1-hexanol	8103	-2.291	-16.347	-14
1-octen-3-ol	18827	-2.465	-16.163	-13.461

Table 2: Docking results of 1-hexanol and 1-octen-3-ol with BACE1 (PDB id: 4IVT).

Compound name	Compound ID	Docking score	Glide emodel	Glide energy
1-hexanol	8103	-0.948	-17.235	-16.441
1-octen-3-ol	18827	-1.267	-16.821	-15.779

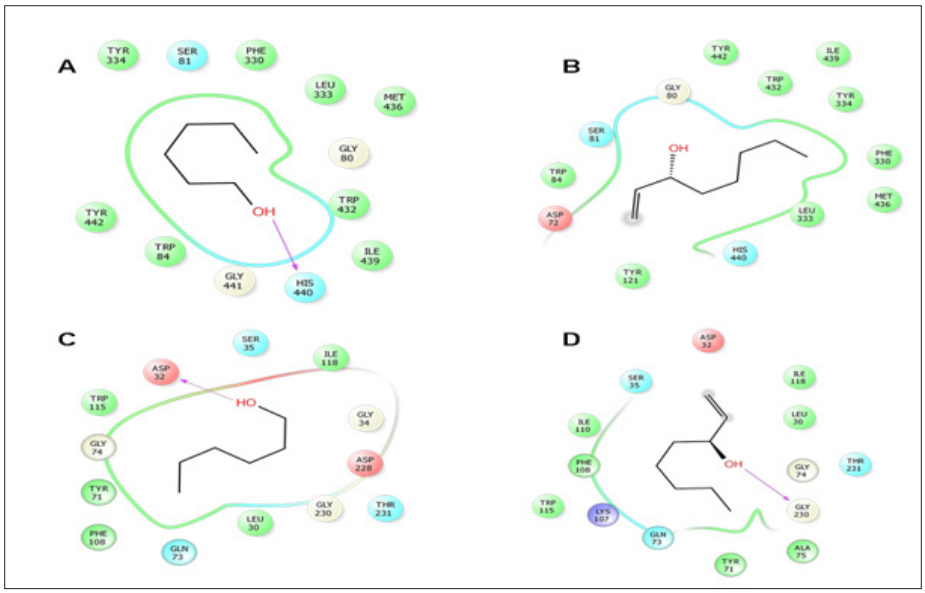

Figure 1: Schematic representation of the interactions between the best pose found for 1-hexanol (A), 1-octen-3-ol (B) with AchE (PDB ID: 2CKM) and, 1-hexanol (C) and 1-octen-3-ol (D) with BACE 1(PDB ID: 4IVT).

The colors indicate the residue (or species) type: Red-acidic (Asp, Glu), Green-hydrophobic (Ala, Val,Ile, Leu, Tyr, Phe, Trp, Met, Cys, Pro), Purple-basic (Hip, Lys, Arg), Blue-polar (Ser, Thr, Gln, Asn, His, Hie, Hid), Light gray-other (Gly, water), and Darker gray-metal atoms. Interactions with the protein are marked with lines between ligand atoms and protein residues: Solid pink-H-bonds to the protein backbone, Dotted pink-H-bonds to protein side chains, Green-pi-pi stacking interactions, Orange-pi-cation interactions. Ligand atoms that are exposed to solvent are marked with gray spheres. The protein "pocket" is displayed with a line around the ligand, colored with the color of the nearest protein residue. The gap in the line shows the opening of the pocket.

Discussion

Phytochemicals are plant-derived chemical compounds that have potential properties. A wide range of phytochemicals has been prevented many chronic diseases, like cancers and heart diseases, by mitigating the cellular dysfunctions [26]. Phytochemicals are the most plenteous dietary antioxidants; but various studies performed in animal models or cell culture demonstrated that the antioxidant activity of these compounds is unlikely to be the sole rationalization for their protecting cellular effects. And phytochemicals even have ability to fix the Alzheimer's disease (AD). Thus, looking out new medication for AD from medicinal plants is not latest. But it is terribly expensive to discover the drugs in laboratory. In silico molecular docking ways will facilitate us to shorten the procedure of drug discovery by choosing the proper drug for the diseases.

The aim of molecular docking is that the accurate prediction of the structure of a ligand inside the constraints of a receptor binding site and to properly estimate the strength of binding. To explore effective drugs for the treatment of AD, completely different compounds against known and novel targets of AD could be designed and investigated using molecular docking. Presently there's no treatment to prevent or cure AD. However, many approved medicines will treat several the symptoms and cause a modest and temporary improvement in memory.

Targeting the direct reason for neuronal degeneration would represent a rational strategy and hopefully provide higher prospects for the treatment of AD. Many molecules for the above-mentioned targets are withdrawn even from the clinical trials either due to their ineffectiveness in human trials or their no specificity for receptors. The brain, being the most complicated organ, is tough in terms of its structural accessibility and therefore the presence of the blood–brain barrier and so tough for several in vitro molecules to be effective in situ. Therefore, special attention ought to be paid for the development of effective ligands against the potent targets of AD [24]. In a very nut shell, molecular modeling and docking would be a promising side for novel drug design and would shorten the time span of drug discovery that might be further explored as potential therapeutic interventions for AD. The above result represents that 1-octen-3-ol showed good docking score between two compounds against both Ach and BACE1. So, 1-octen-3-ol is the best compounds for Ach and BACE1 enzyme inhibition, as it possessed best value in Molecular docking.

Conclusion

The present study revealed that between the compounds 1-octen-3-ol showed best docking score. Further in vivo investigation needs to identify Ach and BACE1 enzyme inhibitory activity of isolated compounds from *L. camara*.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2018.12.002235

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