ORIGINAL ARTICLE

Identification of Possible Molecular Targets of Potential Anti-Alzheimer Drugs by Predicting their Binding Affinities Using Molecular Docking Technique

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Abstract

Objective: The objective of this study was to study the newly selected drug molecule for Alzheimer's disease (AD) which is under clinical trial. **Methods:** The structures were drawn using ChemBioDraw 2D software on the basis of the 1EVE receptor by changing the ligands. Afterward, they were converted to 3D structures using the same ChemBioDraw 3D software in which they were subjected to energy minimization using the MM2 menu and then saved as pdb extension files which can be accessed using the ADT interface. AutoDock Vina (ADT) 1.5.6 software version was used for molecular docking study. **Results:** The selected molecules which are under clinical trial for AD were analyzed by molecular modeling software for identification of activity on different targets. This revealed that three drugs Etozolate, PBT2, and scyllo-Inositol have shown interactions with the 1EVE receptors (acetylcholine esterase) among studied proteins. **Conclusion:** The study has been done by docking, each drug with its original and by cross docking them with different another receptor to determine on what receptor each drug has the greatest affinity. Among these ligands, Etozolate, PTB2, and scyllo-Inositol showed the maximum activity against the 1EVE protein (acetylcholine esterase) with the binding affinities of −8.2, −8.0, and −5.9 Kcal\mol, respectively. This helps in identifying the best possible molecular target for the AD.

Key words: Alzheimer's disease, dementia, molecular docking, molecular targets

INTRODUCTION

Dr. Alois Alzheimer found out a neurodegenerative disorder which is nowadays known as Alzheimer's disease (AD). While examining a brain of a person who had died from an unusual illness, he observed changes in the brain tissue. He found many uncharacteristic clumps such as amyloid plaques (Aβ) and neurofibrillary tangles or tau in the brain.[1] The AD is an irreversible, neurological, and progressive brain disorder in which the brain cells, especially cholinergic neurons start dying that affects memory (destroyed) and intellectual skills of a person. It also affects the ability to perform the simplest tasks in day-to-day life. Alzheimer's symptoms first appear in the people at the age of mid-60s. In the AD, the whole brain size shrinks so that the tissue has increasingly decreased nerve cells and connections. In the postmortem, the brain will always show miniature inclusions in the nerve tissue which is known as plaques and tangles. In the brain, plaques are found between the dying cells and are made up of a protein named beta-amyloid/Aβ. While the tangles are formed from a disintegration of another protein named tau. The abnormal protein clumps are always present with the disease in the brain tissue, but maybe there's another thing that is actually causing this disease.[2] The symptoms involve mental or social behavioral that shows a weakening of "functioning and performing" and affect the ability to perform the daily activities. For example, ability of a person to remember new information worsens, impairments to reasoning, the simple

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Received: 06-02-2018
Revised: 11-03-2018
Accepted: 19-03-2018

task becomes more difficult to perform, improper judgment for exercising, speaking problems, reading and writing, changes in personality, and behavior of the person.[3] The AD is an increasing public health issue among the elder in developing countries. It is projected that by the year 2020, approximately 70% of the world's population aged 60 and above, will be living with an AD in developing countries.[4] According to World Alzheimer Report, King's College London found that there are currently around 47.8 million people living with dementia around the globe, with numbers to be nearly double every 20 years, increasing to 76.7 million by 2030 and 141.5 million by 2050.[5] Research scientist also found that there are more than 9.6 million new cases of dementia occurring each year worldwide that results in one new case every 3.1 s. The report showed that in 2014 nearly 4.6 million of people are living with dementia in India. There are no drugs or treatments that can cure AD completely.[6-8] However, medicines have been developed for an AD that can temporarily alleviate symptoms, or slow down their progression, in some people. However, due to their side effects, there is much need of new drugs. Currently, the U.S. Food and Drug Administration approved five drugs which are used to treat AD symptoms.[9] Three of available drugs, i.e. donepezil, galantamine, and rivastigmine are belongs to "cholinesterase inhibitors" class which proposed to stop the destruction of a chemical messenger in the brain [Figure 1].[10,11] The fourth drug, i.e. memantine regulates the activity of a different chemical messenger in the brain. Therefore, both types of drugs help in the treatment of AD symptoms with a different mechanism. The fifth drug is a combination of donepezil with memantine and showed better potential in the treatment of AD.[12] The current research work is aimed to identify the most probable molecular target of anti-Alzheimer's drugs which are approved or under clinical trials, i.e. Etozolate, PBT2, and scyllo-Inositol and compare with galantamine and donepezil.

METHODS

The current work was aimed to identify the best possible target of new drug molecule for AD. For this purpose, the databases of various ligands were prepared and geometry, as well as energy, was minimized through ChemDraw program.[13] All the optimized ligands were saved in pdb format. Protein structures were downloaded from protein data bank[14] and prepared before docking to add hydrogen atoms, optimize hydrogen bonds, remove atomic clashes, and perform other operations by selecting the protein chain, heteroatoms, ligands, and waters present in pdb file. Setup the docking parameters and started docking calculations by selecting protein and ligand from the library and by analyzing the interactions betwee n protein and ligand.[15-17] Analyses of results were carried out by comparing binding affinity toward the receptor.

RESULTS AND DISCUSSION

The main purpose of this study is to identify the possible molecular target anti-Alzheimer's drugs by studied them to target proteins (receptors). Various molecular targets were selected, i.e., 1W6R, 1EVE, 5DEX, 5TP9, and 2W08 and studied for Etozolate, PBT2, and scyllo-Inositol were compared with galantamine and donepezil as shown in Figure 2.

The selected molecules which are under clinical trial for AD were studied by molecular modeling software for identification of their binding affinity on different targets. This revealed that some molecules showed the high binding affinity with 1EVE (acetylcholine esterase) among studied

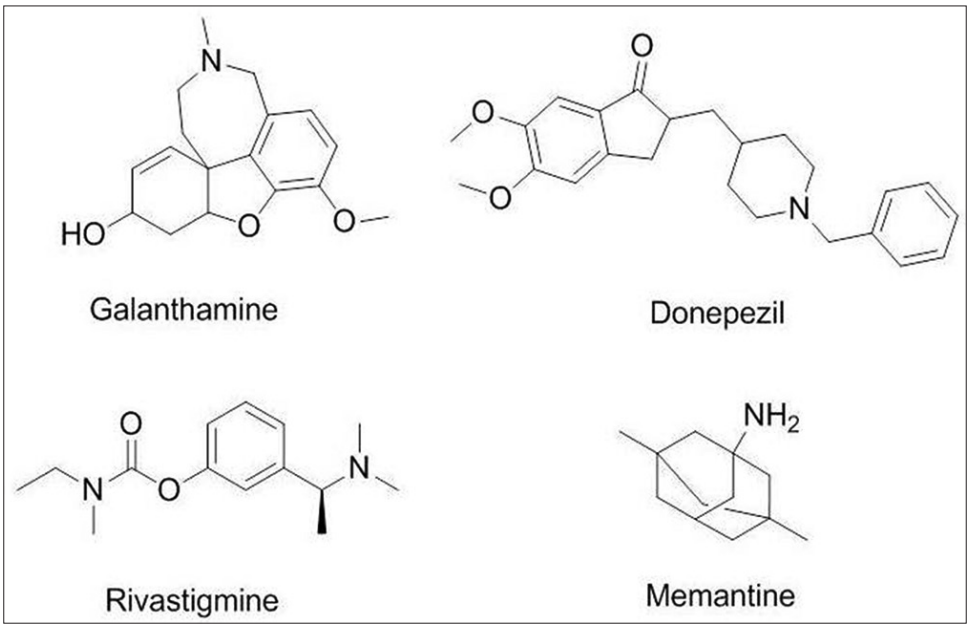


Figure 1: Common anti-Alzheimer's agents

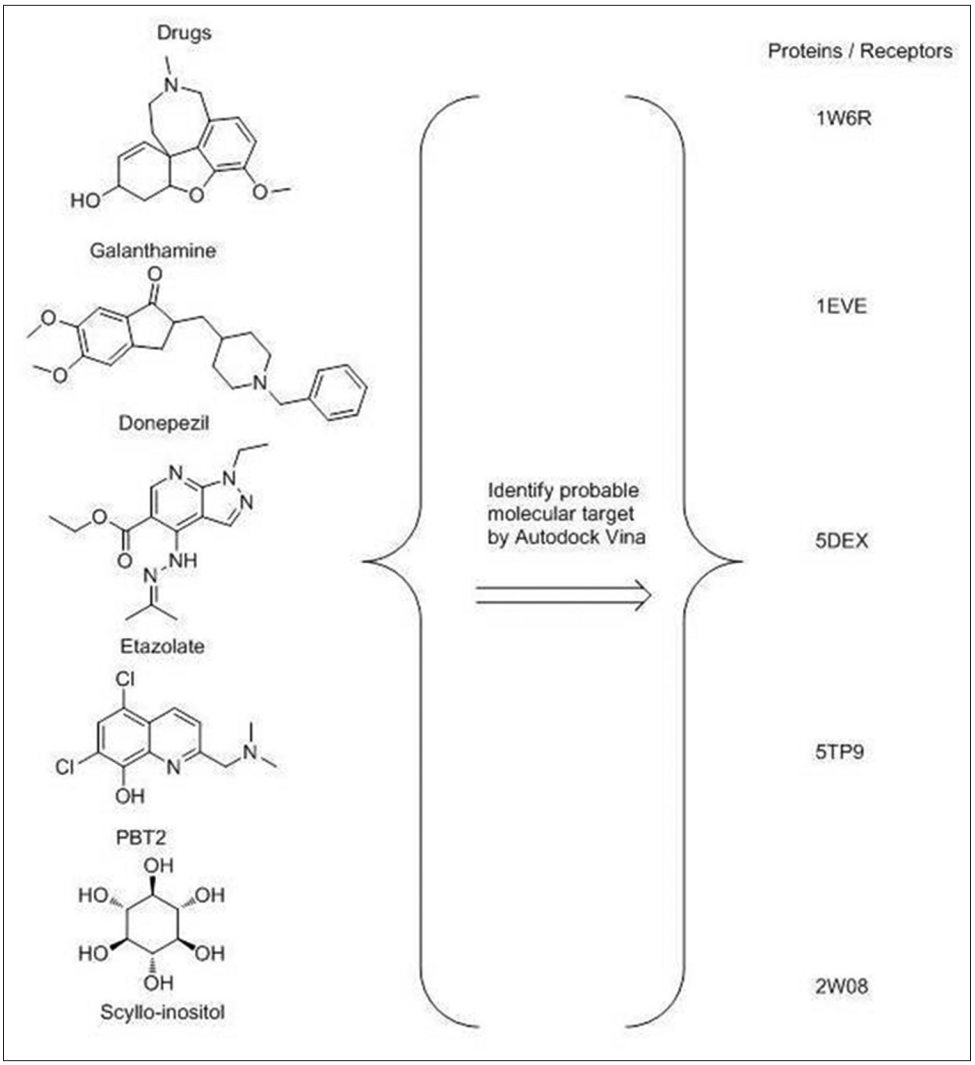


Figure 2: Selected anti-Alzheimer drugs to identify the possible molecular target

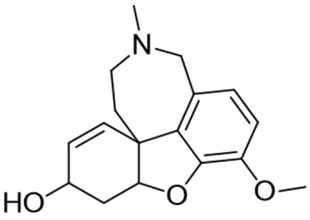
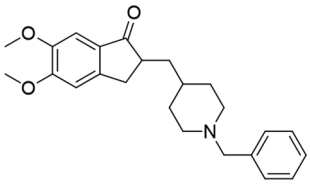
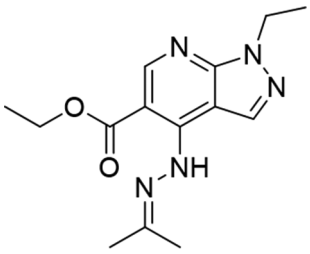
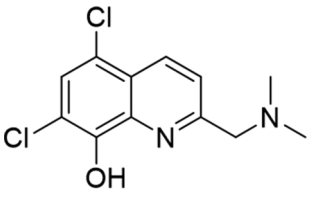
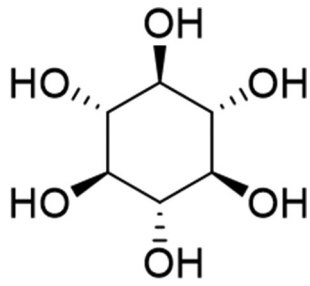
proteins. First, the validation of protein was done by extraction of ligand and docking it in the same manner as an actual ligand Etozolate (E20). This could be achieved by ligand preparation for docking studies through the addition of polar hydrogens, detecting root [Figure 3], and converting it to pdbqt extension file. Protein preparation was the next step after the extraction of ligand. Protein was prepared by removing water molecules, repairing missing atoms, adding polar hydrogens only, and subsequently adding the Kollman charges. Further, the grid box was generated keeping the ligand as a center.

From grid output file, the configuration file "conf.txt" was prepared and command prompt was used for Autodock Vina molecular docking by giving command "program files\ the Scripps research institute\vina\vina.exe --config conf. txt --log log.txt." It generated the output file with the docking score or binding affinity (Kcal/mol); similarly, all the drug molecules were studied on various proteins and their binding affinities are represented in Table 1.

All three drugs Etozolate, PBT2, and scyllo-Inositol were studied for their binding interaction and compared with approved drug galantamine and donepezil which is discussed in detail below. The study of the binding interaction of Etozolate, PBT2, and scyllo-Inositol by molecular docking showed that Etozolate, PBT2, and scyllo-Inositol had more affinity with 1EVE receptor with −8.2, −8.0, and −5.9 Kcal/mol, respectively. This is revealed by a cross-docking study of each ligand with different AD targets by analyzing their binding affinity.

Ligand Etozolate showed better binding affinity with 1EVE receptor/protein. Etozolate shows affinity −7.9, −8.2, −7.2, −7.8, and −5.7 Kcal/mol with 1W6R, 1EVE, 5DEX, 5TP9, and 2W08 proteins, respectively. The affinity of Etozolate for 1EVE was found to be −8.2 Kcal\mol. It showed favorable interaction such as the A ring (pyridine) of the drug involved in hydrophobic interaction with PHE330 and the ring B (imidazole) showed aromatic interaction with TYR334. Hydrazine alkyl showed hydrophobic interaction with ASP72 and NH of hydrazine showed hydrogen bonding interaction with TYR121 and TYR70 [Figure 4].

Table 1: Comparison of different drugs at different target receptors

Drugs	Binding affinity (Kcal\mol) on receptor				
	1W6R	1EVE	5DEX	5TP9	2W08
 Galantamine	−10.6	−9.7	−7.0	−6.9	−6.0
 Donepezil	−9.9	−10.9	−8.1	−7.8	−6.6
 Etozolate	−7.9	−8.2	−7.2	−7.8	−5.7
 PBT2	−7.7	−8.0	−6.9	−7.7	−5.3
 Scyllo-Inositol	−5.7	−5.9	−5.8	−5.6	−4.4

PBT2 is the other ligand which showed better potential activity against the 1EVE protein of AD [Figure 5]. PBT2 shows affinity of −7.7, −8.0, −6.9, −7.7, and −5.3 Kcal/mol with 1W6R, 1EVE, 5DEX, 5TP9, and 2W08 proteins, respectively.

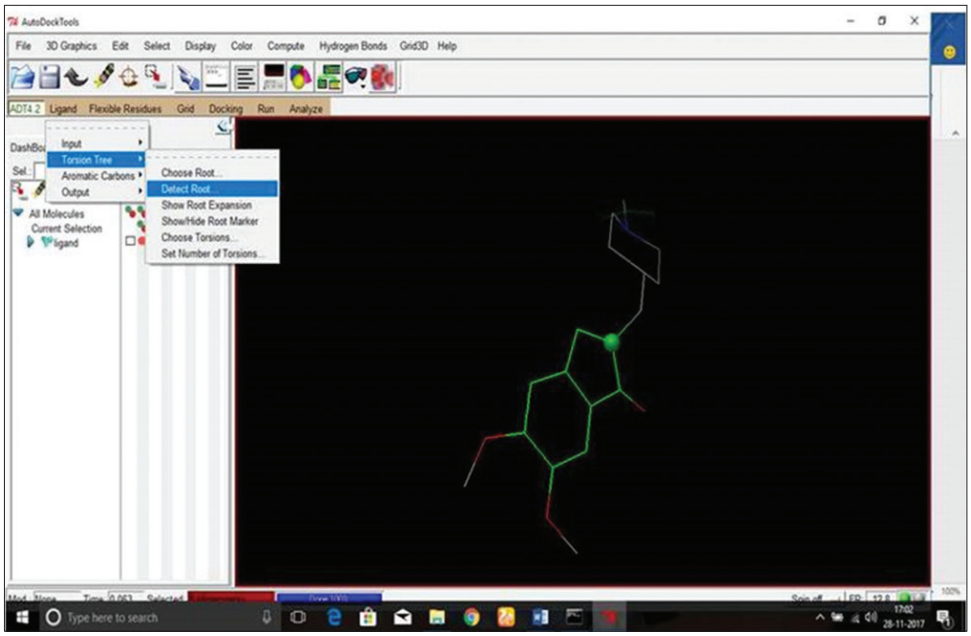


Figure 3: Extraction and detect root using Autodock Vina

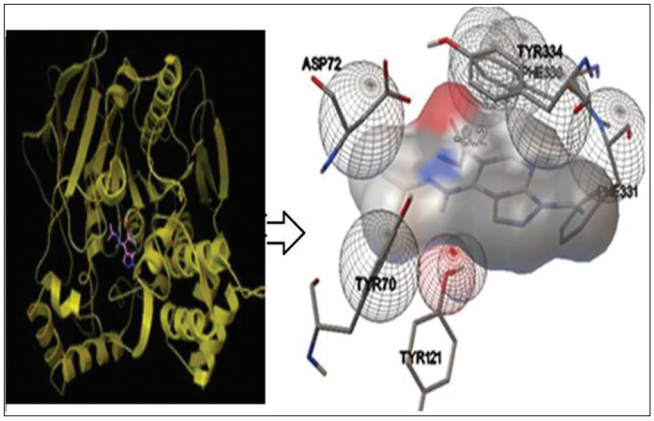


Figure 4: Interaction of Etozolate with 1EVE protein

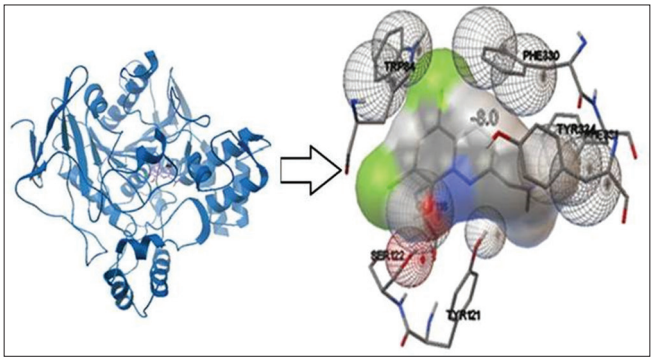


Figure 5: Interaction of PBT2 with 1EVE protein

The affinity of PBT2 for 1EVE was found to be −8.0 Kcal\mol. Most favorable interactions are included SER122 involved in hydrogen bonding with the hydroxyl group of ring A (phenolic) and the TRP84 is associated with halogen bonding with the chloro group of ring A (phenolic) and TYR324 interacts with N,N-dimethyl group attached to B ring (pyridine).

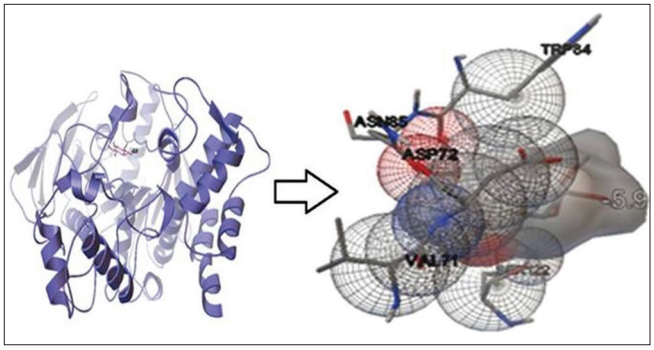


Figure 6: Interaction of scyllo-Inositol with 1EVE protein

Scyllo-Inositol shows affinity of −5.7, −5.9, −5.8, −5.6, and −4.4 Kcal/mol with 1W6R, 1EVE, 5DEX, 5TP9, and 2W08 proteins, respectively. Scyllo-Inositol showed potential binding affinity to a 1EVE protein found to be −5.9 Kcal\mol. Some of the favorable interaction is like ASP85 involved in hydrogen bonding with a hydroxy group of the ring and another part also interacts with ASP72 [Figure 6]. Hence, by observing the binding affinities, we can propose and identify the target of Etozolate, PTB2, and scyllo-Inositol which showed good binding affinity to 1EVE protein.

CONCLUSION

The current work is undertaken to find out a better possible molecular target of anti-Alzheimer drugs under Phase III clinical trials and comparison with currently used drugs on the market. The study has been done by docking, each drug with its original and by cross docking them with different another receptor to determine on what receptor each drug has the greatest affinity. Among these ligands, Etozolate, PTB2,

and scyllo-Inositol showed the maximum affinity to 1EVE protein (acetylcholine esterase) as a most probable target, which is predicted with −8.2, −8.0, and −5.9 K cal\mol binding affinity, respectively. The analyses of the interaction of drugs with their respective protein were also done, and the favorable interactions were shown by these molecules on their respective receptor.

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Source of Support: Nil. **Conflict of Interest:** None declared.