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Virtual Screening of Solanine and its derivatives to analyze inhibitory activity towards Acetylcholinesterase for the treatment of Alzheimer's disease

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Abstract:

Alzheimer's disease (AD) is most common form of dementia affecting elderly people, and sixth leading cause of death worldwide. The two abnormal structures formed in AD patient's brain are beta-amyloid plaques and neurofibrillary. The beta-amyloid plaque formation is accelerated due to acetylcholinestarases. Treatment of AD has majorly dependent on inhibition of acetylcholinestarase. In the present study, acetylcholinesterase receptor is docked with solanine and its derivatives and with a commercially available drug. The lead 3 compounds, are selected based on minimum binding energy and interaction with the active site of the receptor, are much better compared to commercially available drug. Molecular interactions of the receptor complexes with lead solanine compounds are also found to be higher in number. By this it can be hypothesize that solanine derivatives can inhibit acetylcholinesterase more effectively, which controls rapid breaking of acetylcholine, a neurotransmitter to acetyl and choline and aid in Alzheimer's treatment.

Key words: Alzheimer's disease, Acetylcholinesterase receptor, Solanine, Donepezil, Neurotransmitter, Dementia, Docking

Introduction

Alzheimer's disease (AD) is most common form of dementia affecting elderly people, and sixth leading cause of death worldwide. AD is characterized by weak memory, changes in behaviour, inability to recognize languages and loss of IQ, is a very complex and progressive neurodegenerative disease (Ferri CP et al., 2005, Birks J, 2006, ADEAR, 2013). Many pathological conditions indicate symptoms of AD, such as improper functioning of cholinergic system, halted functioning of homeostasis of biometals and increased accumulation of beta-amyloids (Zhou, X. et al., 2010, Tang, H. et al., 2007). The two abnormal structures formed in AD patient's brain are beta-amyloid plaques and neurofibrillary (Mattson, 2004).These

beta-amyloid plaque formation is accelerated due to acetylcholinestarases enzyme; biochemical studies explain (Inestrosa, 2008). Thus development of effective treatment for AD has majorly dependent on inhibition of acetylcholinestarases (Peter J H et al., 2006, Maheshwari U, 2010).

Acetylcholinesterase enzyme hydrolyses the neurotransmitter acetylcholine very rapidly and completely stops neurotransmission at synaptic cleft (Hay D et al., 2010). Acetylcholinesterase inhibitors are the standard of therapy and are the only class of drugs approved by the Food and Drug Administration (FDA) to treat AD patients (Cummings JL, 2003). Donepezil is the first market available drug to treat AD, is not much effective in modulating disease process and shows most common side effects like dizziness, cramps, fatigue, diarrhoea despite of its specificity to acetylcholinesterase (Mark H et al., 2002), which encourages to discover new acetylcholinesterase inhibitors.

Solanine, belongs to solanaceae family is a glycoalkaloid and poisonous in nature. It is present in all parts of the plant. Solanine shows pesticidal and fungicidal effects as a defend mechanism. First time it was extracted by desfosses from the berries of the European black nightshade Solanum nigram in 1820 (Desfosses, 1820). Solanine has an inhibitory activity towards cholinesterases (Harries et al., 1962; McGchee et al., 2000). It helps in acetylcholine breakage into acetyl and choline by inhibiting the fast production of acetylcholinesterases, which maintains the level of acetylcholine, a neurotransmitter and ultimately treats AD.

Docking of macromolecule with ligands aids in predicting the intermolecular interaction of the complex formed, which plays very important role in development of new drugs. Molecular interaction studies help in understanding the modification in functioning of macromolecule upon interaction with ligand. Autodock4 provides very good results of docking of

ligand in cavity of the macromolecule when compared with experimental data. The aim of the study is to retrieve the potential free energy and molecular interactions from complex formed between receptor human acetylcholinesterase and solanine and its analogous obtained by Autodock4, Compare these results with complex of receptor human acetylcholinesterase with donepezil, a market available acetylcholinesterase inhibitor.

Methodology

The protein Data Bank (PDB), a single worldwide archive of structural data of biomolecules, was established in 1971 at Brookhaven National Laboratories (Berman et al., 2000). It contains X- ray crystallography and NMR method determined structural records of the macromolecules. The database is maintained by Research collaboratory for structural bioinformatics (RCSB), as on Apr 08, 2014 PDB has 99293 macromolecular structures data entries.

The Crystal structure of receptor human acetylcholinesterase, PDB ID 3LII, molecular weight 120180.53 is obtained from PDB database, see figure1. The structure is determined using X-ray diffraction method, having 3.20 Armstrong resolutions. It consists of two amino acids chains A and B, have unique sequences. Length of each chain is 540 amino acids. There are 24 helices and 25 strands in the structure. The additional ligands which are present along with the structure are removed using Chimera, a visualization system for exploratory research and analysis (Pettersen et al., 2004). The structure is energy optimized using Discovery Studio 2.0, a molecular modelling environment (need citation)

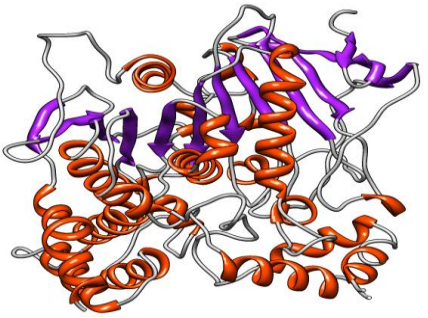

Figure1-Acetylcholinesterase Chain-A

The PubChem Compound, a database for validated chemical structures information. The structures stored in this are pre-clustered and cross-referenced based on their identity and similarity. The structure of donepezil Pubchem ID CID 3152 and solanine with PubChem ID CID 262500 and 76 other compounds similar to it, are retrieved from PubChem Compound Database. Molecular weight of these compounds ranges from 379.49 [g/mol] to 1192.34 [g/mol].

The minimum energy with most stable conformations of these compounds are computed using Avogadro, a software for advanced semantic chemical editing, visualization, and analysis (Marcus D Hanwell et al., 2012), which are used in docking with macromolecule.

Autodock is most widely used open source docking software in structure based analysis and prediction of biomolecular complexes. It has a set of protocols to pre-process the macromolecules and the small compound to make them suitable for docking, which involves deciding the atom type, hydrogen addition/removal, file format conversion, grid parameter and dock parameter setting. Autodock implies Lamarckian Genetic Algorithm along with empirical free energy force field to predict the highly stable bonded conformations with maximum free energies of associations (Morris, G. M., et al., 2009).

In this study protein-ligand rigid docking, a unique method of docking of ligand to the known active site of protein is used. The macromolecule with PDB ID 3LII and solanine and its analogues are loaded to the software one at a time and the series of protocols are applied to obtain the most stable binding poses.

Computation of number of hydrogen bond interactions using Chimera and poses with minimum binding energies for each complex, are saved in a tabular form (table 1). To visualize the interactions in the complex Ligplot, a software program to generate schematic diagrams of protein-ligand interactions is used (Wallace A C et al., 1995).

Results and Discussions

The receptor human acetylcholinesterase has chain A and chain B, are sequence unique with same binding pocket, due to which only one chain (chain A) is used for docking (see figure 1). Molecular docking of receptor with the ligands has been very challenging task to predict the binding energies.

The docking results of 78 receptor-ligand complexes shows that the binding energies are in the range of -11.89kcal/mol to +1556.25kcal/mol, with minimum binding energy being -11.89 kcal/mol. The lead 3 compounds, PubChem ID CID 25245074, CID 25245075, CID 5351499 with binding energies -10.77kcal/mol, -10.11kcal/mol, -9.22kcal/mol respectively are selected based on minimum binding energy and at the active site residue Phe295 of the receptor, are much better compared to market available drug donepezil (PubChem ID CID 3152) with binding energy -6.94kcal/mol, see figure 2,3,4,5. Number of hydrophobic interaction in receptor complexed with these lead compounds are higher than donepezil, which are listed in table 1. These interactions can be seen in figure 6,7,8,9. The interacting residues in these complexes are listed in table 2.

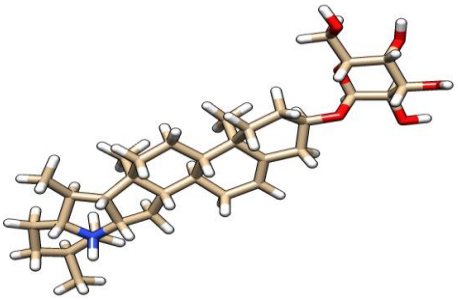

Figure2 – Chemical structure of Gamma – solanine (Pubchem ID - CID 25245074)

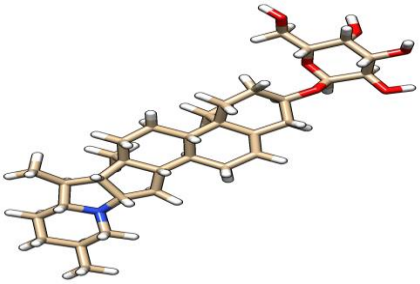

Figure3 - Chemical structure of CID 25245074

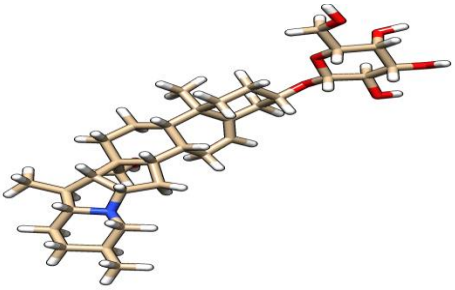

Figure4 - Chemical structure of Isorubijervosine (Pubchem ID - CID 25245075)

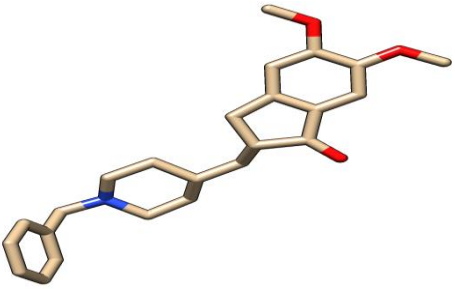

Figure5 - Chemical structure of Donepezil (Pubchem ID - CID 3152)

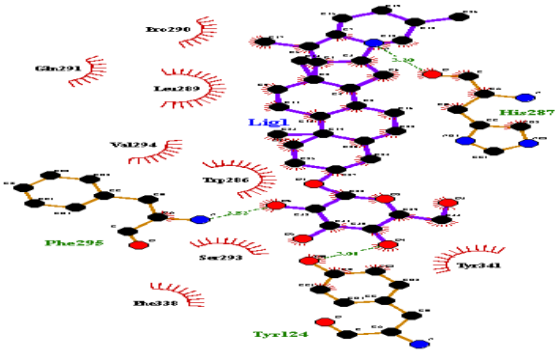

Figure6 - Interaction of Acetylcholinesterase – Solanine analogue (PubChem ID - CID 25245074)

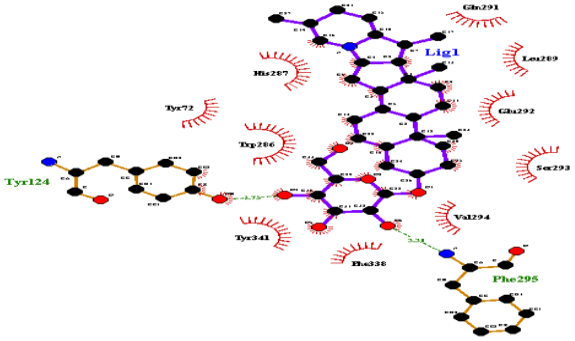

Figure7 - Interaction of Acetylcholinesterase – Solanine analogue (PubChem ID – CID 25245075)

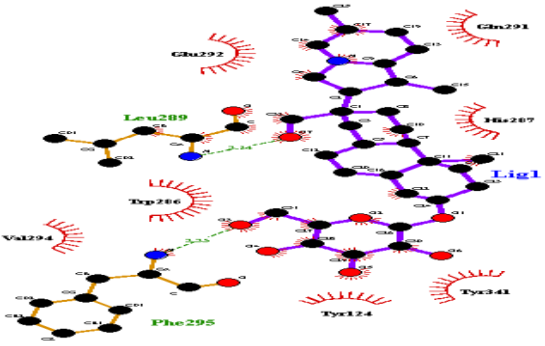

Figure 8 - Interaction of Acetylcholinesterase – Solanine analogue (PubChem ID - CID 5351499)

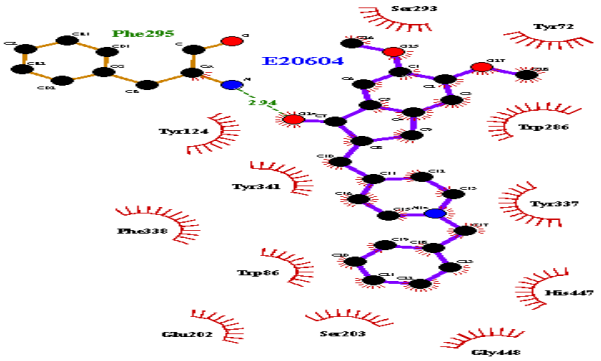

Figure 9 - Interaction of Acetylcholinesterase – Solanine analogue (PubChem ID - CID 5351499)

Table 1 - List of top 3 solanine analogoues and donepezil with binding energy and no. of hydrogen bonds

Compound Name	**PubChem ID**	**Binding Energy**	**No. of hydrogen bonds**
Gamma - solanine	CID 25245074	-10.77	11
----------	CID 25245075	-10.11	9
Isorubijervosine	CID 5351499	-9.22	11
Donepezil	CID 3152	-6.71	7

Table 2 – List of interacting residues in Acetylcholinesterase complexed with top 3 solanine analogues and donepezil

Receptor	**Compound Name**	**PubChem ID**	**Interacting Residues**
Acetylcholinesterase (PDB ID - 3LII)	Gamma – solanine	CID 25245074	Tyr124, Trp286, His287, Leu289, Gln291, Glu292 Val294, Phe295, Tyr341
	--------- ---------	CID 25245075	Tyr72, Tyr124, Trp286, His287, Leu289, Gln291 Glu292, Ser293, Val294 Phe295, Phe338,

			Tyr341
	Isorubijervosine	CID 5351499	Tyr124, Trp286, His287, Leu289, Pro290, Gln291 Ser293, Val294, Phe295 Phe338, Tyr341
	Donepezil	CID 3152	Tyr72, Trp86, Tyr124, Glu202, Ser203, Trp286 Ser293, Phe295, Tyr337 Phe338, Tyr341, His447 Gly448

Conclusions

Protein-ligand interaction is crucial part of drug designing. In the study, receptor human acetylcholinesterase is docked with ligand solanine and its analogues in search to find anti-acetylcholinesterase molecule cheaper, largely accessible from nature with lesser side effects in contrast to chemically synthesized drugs like donepezil for treating Alzheimer's disease. Autodock4 tool is used to retrieve the most precise binding poses and higher number of molecular binding interactions between receptor human acetylcholinesterase and solanine and its analogous. The interactions visualized using LigPlot software shown to be very much stable, which lets to hypothesize that solanine analogues can inhibit acetylcholinesterase more effectively, which will control rapid breaking of acetylcholine, a neurotransmitter to acetyl and choline and treat AD patients.

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