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RESEARCH **P**APER

Binding pattern determination for class of anti-alzheimer's compound

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Alzheimer's disease (AD) is the most common form of dementia. No cure has been observed for the disease, and it worsens as it progresses, which eventually leads to death. It is believed that some plaques and tangles develop within the structure of the brain which causes brain cells to die. Alzheimer's patients also have a deficiency of neurotransmitters which ultimately hampers the transmission of messages in the brain. It was confirmed by *Amyloid hypothesis*that beta-amyloid (βA) deposits are the fundamental cause of the disease. So, in this research natural and synthetic compounds were selected on the basis of their binding or inhibition to the amyloid precursor protein (APP). The protein and the ligands were optimized, docked and their interaction was visualized on the basis of binding energy.

Key words : Alzheimer's, Amyloid, Docking, Binding energy

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INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia (Sabiha *et al.,* 2015). This diseases progresses until death and no cure could occur in this disease. The symptoms include memory loss, language problems and unpredictable behaviour (Desgranges *et al.,* 1998). Many abnormal clumps (also called amyloid plaques) and tangled bundles of fibres (also called neurofibrillary tangles) are found in brain (Selkoe, 2000). Amyloid plaque is majorly formed from amyloid-beta-peptide (Aβ), which is derived from APP (Younkin, 1998). It is found mostly over 65 years of age (Hebert *et al.*, 2001). Protein structure prediction is one of the most important goals persued by bioinformatics. With this, the 3 dimensional structure of protein can be predicted easily from their amino acid sequences. For preserving the protein activity, prediction process is essential. The 3D structure of protein gives deeper knowledge of the protein than its sequence. Thus, researchers have been trying for long to get the protein structure. The protein structure helps to find out its function and thus in the development of drugs. In computational biology, "Homology modelling" is one of the most reliable technique for building the 3D model of a protein of unknown structure from one or more related proteins of known structure (Read *et al.*, 1984). The major goal of this research is to understand the relationship between amino acid sequence with 3 dimensional structures in proteins and how drug molecule is docked in proteins. If the relationship one known, then the structure of the protein could be reliably predicted from the amino acid sequence and the disease protection drug can be predicted. For drug discovery, many

computational methods are used like QSAR, virtual screening and structure based drug designing (SBDD) methods. Among all of these, SBDD is gaining much importance due to current growth of structural data available in Nucleic Acid Data Bank and RCSB. These structures can then be used in molecular modeling for designing lead molecules based on the structural features of the active sites. SBDD aims to create a drug molecule that can bind specifically to the active site of the target enzyme, thereby preventing the normal chemical reaction to occur and ultimately halting the progression of the disease. These drugs work by regulating neurotransmitters (Francisco *et al.*, 2015), the chemicals that transmit messages between neurons. They may help maintain thinking, memory, and speaking skills, and may help with certain behavioural problems. The objective of the present work was to dock the targeted protein and the corresponding ligand and visualize the binding pattern for Anti-Alzheimer's compound and choosing the best among them for further use.

RESEARCH METHODOLOGY

Target selection :

Target for Alzheimer disease was identified using literature review and information like entry name, gene name, accession number was retrieved in Uniprot KB.

Template selection :

Template was selected by performing alignment using BLAST. The reference database used was PDB. The protein with maximum similarity was selected as template. By analysing the BLAST results, the protein having similarity between 30 per cent-70 per cent was selected and its structure was downloaded from PDB.

Protein modelling using SPDBV and modeller :

Swiss-Pdb Viewer and modeller were used to obtain the final protein which was used for further analysis.

Model validation :

SAVS (Structural Analysis and Validation Server) is a server used for model validation and for analysing protein structures for validity and assessing how correct they are. In this, Ramachandran plot was obtained and the output of best one, *i.e.*, either of SPDBV or Modeller was saved for later use.

Ligand selection :

The ligands (natural and synthetic) were selected from various research articles like pubchem, zinc database and binding database. 5 natural and 15 synthetic ligands (isomer of ligands available in market) were collected and its structure was drawn on chemsketch. These structure files were then converted to Pdb file using World wide molecular matrix (Open Babel) tool.

Molecular docking using AUTODOCK :

AUTODOCK4 was used to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure. Commands for AutoDock were given in Cygwin.

RESEARCH FINDINGS AND ANALYSIS

The target protein obtained from Swiss Prot and modeller can be viewed through Ramachandran plot as shown in Fig. 1 and 2. The program that has the more percentage of residues in most favoured regions was selected.

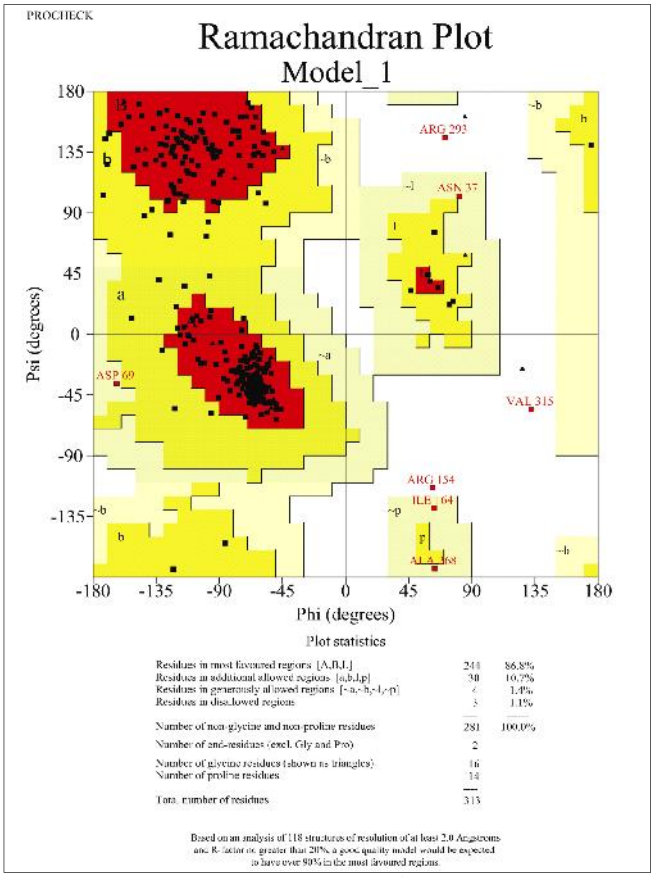

Fig. 1: Ramachandran plot obtained from SWISS-PROT

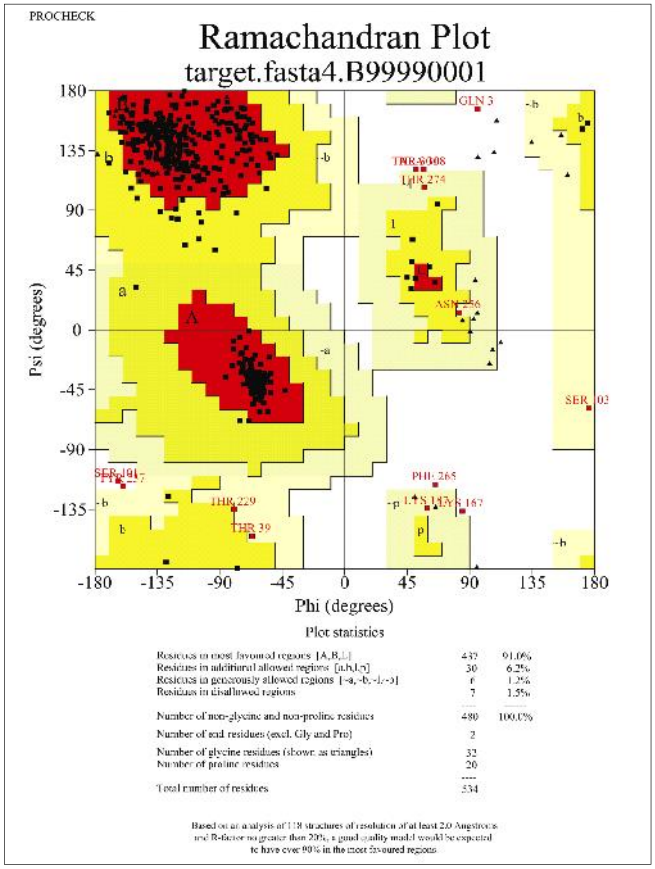

Fig. 2 : Ramachandran plot obtained from modeller

As it can be seen in Ramachandran plot, that percentage residues in most favoured regions is approx 90 per cent in case of modeller, so, for our further studies we choose the target designed by the modeller rather than choosing the target from SPDBV *i.e.* SwissProt.

For further study on protein orientation and to predict the affinity, activity, binding orientation of our ligand to our target protein, we perform docking using AUTODOCK. Results were obtained in glg and dlg files which clearly show the lowest and the mean binding energy which was required for research (Fig. 3).

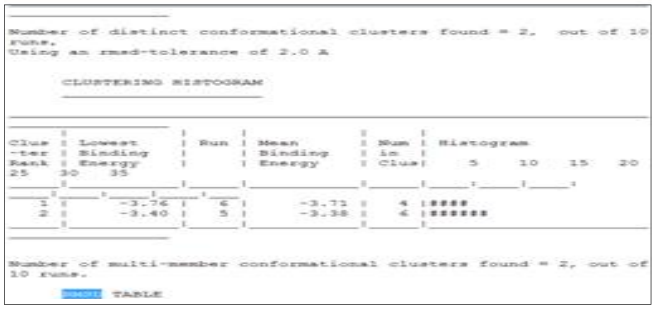

Fig. 3 : GLG file obtained from AUTODOCK showing binding energy for the PDB ID-1Y8Q

Table 1 : Binding energy table

Sr. No.	TARGET	PDB ID	INHIBITORS	TYPES	ENERGY
1.	TARGET.FASTA1	4DON	DONEPEZIL	1	-1.53
				2	-1.75
				3	-1.75
			GALANTAMINE	1	-3.79
				2	-3.58
				3	-3.57
			MEMANTINE	1	-3.48
				2	-3.51
				3	-3.33
				MAIN	-3.64
			TACRINE	1	-3.51
				2	-3.91
				3	-3.62
				MAIN	-3.48
2.	TARGET.FASTA2	3PMR	DONEPEZIL	1	-2.38
				2	-2.38
				3	-2.38
			GALANTAMINE	1	-5.24
				2	-5.04
				3	-5.00
			MEMANTINE	1	-4.68
				2	-4.70
				3	-4.51
				MAIN	-4.83
			TACRINE	1	-4.66
				2	-4.93
				3	-4.64
				MAIN	-4.65
		3Q7G	DONEPEZIL	1	-3.56
				2	-3.58
				3	-3.57
			MEMANTINE	1	-6.47
				2	-6.47
				3	-6.20
				MAIN	-6.70
3.	TARGET.FASTA3	3Q7G	DONEPEZIL	1	-3.56
				2	-3.57
				3	-3.57
			GALANTAMINE	1	-6.38
				2	-6.31
				3	-6.27
		3UMH	DONEPEZIL	1	-3.15
				2	-3.16
				3	-3.12
			GALANTAMINE	1	-5.93
				2	-5.28
				3	-5.27

Table 1 : Contd……..

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4.	TARGET.FASTA4	1Y8Q	DONEPEZIL	1	-4.16
				2	-4.11
				3	-4.11
			GALANTAMINE	1	-4.73
				2	-3.76
				3	--3.74
			MEMANTINE	1	-6.13
				2	-6.17
				3	-6.57
				MAIN	-6.35
			TACRINE	1	-5.20
				2	-4.78
				3	-3.66
				MAIN	-3.63
		1YOV	DONEPEZIL	1	-2.39
				2	-2.38
				3	-2.38
			GALANTAMINE	1	-5.17
				2	-4.85
				3	-4.82
			MEMANTINE	1	-4.92
				2	-5.00
				3	-4.63
				MAIN	-4.68

Table 1 : Contd……..

Table 1 : Contd……

			TACRINE	1	-4.93
				2	-5.34
				3	-4.88
				MAIN	-4.87
5.	TARGET.FASTA5	1TKN	DONEPEZIL	1	-2.14
				2	-2.13
				3	-2.13
			GALANTAMINE	1	-5.28
				2	-4.75
				3	-4.75
			MEMANTINE	1	-4.85
				2	-4.81
				3	-4.57
				MAIN	-4.90
			TACRINE	1	-4.45
				2	-4.94
				3	-4.46
				MAIN	-4.40
		3UMH	DONEPEZIL	1	-3.15
				2	-3.16
				3	-3.12
			GALANTAMINE	1	-5.93
				2	-5.28
				3	-5.27

The overall result of binding energy obtained from interaction between various PDB IDs and various inhibitors and their isoforms using AUTODOCK are shown in Table 1.

Conclusion :

Knowledge of protein structure is useful as it provides information about target site and various inhibitors that can be used in the field of drug development. Homology modeling and Autodock are the powerful techniques which provides faster and cheaper insilico rate of drug designing. They make the research task less cumbersome as large amount of data can be handled easily.

The drug with minimum binding energy, *i.e.*, memantine is most stable and can be used for further analysis.

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