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Molecular Docking Studies on the Interaction of Anti-Alzheimer Compounds with Amyloid Beta Peptides

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***Abstract*—Alzheimer's disease (AD) is an irreversible, progressive neurodegenerative disorder that slowly affected to the loss of memory and the ability to perform simple cognitive activities. Amyloid Beta (Aβ) peptide catalysed by β- and γ-secretases is the main hypothesis of AD progression that is associated with synaptic failure in brain. The $A\beta_{1-42}$ is the most prevalent form of Aβ peptides that have been suggested as a primary key in AD. Molecular docking studies have been performed to investigate the interaction of Aβ with nine molecules, which were found to exhibit amyloid inhibitory effect. We found that folic acid and donepezil compounds showed high binding afinity in both $A\beta_{42}$ peptide (PDB ID: 1IYT and 1Z0Q), in comparison to the other ligands. The binding interactions of folic acid and donepezil compounds with active site of Aβ protein model suggested that the amino acid residues of Glu11, Phe19, Gln15, Glu22 and Val12 play a key role for drug design.**

Keywords—molecular docking, amyloid βeta peptide, hydrogen bonding, Alzheimer's

Introduction

Alzheimer's disease (AD) is a neurological disorder characterised by the aggregation of amyloid beta (Aβ) protein into fibrillary amyloid plaques in the brain. The Aβ peptide is the product of amyloid precursor protein (APP) proteolysis, mostly composed of 42 amino acids ($A\beta_{1-42}$) sequence [1]. The $A\beta_{42}$ produced small neurotoxic oligomers, which is the main pathogenic peptide in AD. Thus, the inhibition of Aβ peptide is one of the strategy in designing potential drug for AD therapy.

This study was aimed to analyze the interactions of two forms of $A\beta_{42}$ peptide with nine ligands. Five molecules were selected based on their reported inhibitory effect on Aβ either *in vitro* or *in vivo* which are good candidates for AD treatment. These compounds are curcumin, folic acid, ibuprofen, rosmarinic acid and ascorbic acid. The rest were drugs approved by the U.S. Food and Drug Administration (FDA) to treat Alzheimer's patients. Current drugs for AD such as donepezil, galantamine, rivastigmine and tacrine are acetylcholinesterase inhibitors that can treat some symptoms but not to cure the disease.

Ibuprofen as a non-steroidal anti-inflammatory drugs has been found to control the Aβ aggregation [Zurita, 2013]. Natural compounds such as curcumin, folic acid, rosmarinic acid and ascorbic acid are nontoxic with high anti-oxidant properties [Rebekah, 2015]. Both curcumin and rosmarinic acid compounds have been found to inhibit the formation of amyloid fibril *in vitro* [2]. Recently, folic acid has been examined to improve cognition and inflammation markers on AD patients [Chen, 2016]. Other study reported that ascorbic acid was found to reduce amyloid plaque burden *in vivo* [Kook, 2014].

Although some compounds including curcumin and folic acid are under clinical trial phase, their binding interactions with Aβ peptides have not yet been understood at the molecular level. Computer simulation such as molecular docking has been successfully used for studying protein-ligand interaction and virtual screening. Molecular docking was performed between aminopeptidase (SGAK) with 1IYT peptide showed that Glu139 might play an important role to degrade Aβ peptide [Dhanavade, 2014]. AutoDock Vina was applied to investigate the binding of ergothionein and selenoergothionein as a potential inhibitor against 1IYT peptide [Saddala, 2016]. The interactions of anti-amyloidogenic behaviour of 40 small molecule inhibitors with $A\beta_{1-40}$ and Iowa mutant $D_{23}N\text{-}A\beta_{15-42}$ peptides and their modes of binding have been studied using molecular docking approaches [Khan, 2019].

Docking results are very useful to predict the behaviour of the compounds in the binding site of targets as well as to explain fundamental biochemical processes [3]. Here, AutoDock Vina was used for studying the binding interaction of nine compounds including curcumin, donepezil, folic acid, galantamine, ibuprofen, rosmarinic acid, rivastigmine, tacrine and ascorbic acid. The docking complexes were analysed based on their binding pose, binding afinity and interaction.

Methodology

Protein preparation

The three-dimensional (3D) structure of the $A\beta_{42}$ peptide in a polar environment (PDB ID: 1IYT)

(Crescenzi, 2002) and apolar environment (PDB ID: 1Z0Q) (Tomaselli, 2006) were taken from the Protein Data Bank (PDB) (http://www.rcsb.org/pdb).

Ligand preparation

The structures of all the compounds in TABLE I were obtained from PubChem database [4] in SDF format and converted into PDB using Discovery Studio Visualization [5] for further docking studies. The structures were minimised using general AMBER force field (GAFF) in Avogadro software [6].

TABLE I. THE MOLECULAR STRUCTURE AND MOLEULAR WEIGHT OF LIGANDS

Ligand Compounds	PubChem ID	Molecular Formula	Molecular weight (g/mol)
Curcumin	969516	$C_{21}H_{20}O_6$	368.40
Donepezil	3152	$C_{24}H_{29}NO_3$	379.50
Folic Acid	135398658	$C_{19}H_{19}N_7O_6$	441.40
Galantamine	9651	$C_{17}H_{21}NO_3$	287.35
Ibuprofen	3672	$C_{13}H_{18}O_2$	206.28
Rosmarinic acid	5281791	$C_{18}H_{16}O_8$	360.31
Rivastigmine	77991	$C_{14}H_{22}N_2O_2$	250.34
Tacrine	1935	$C_{13}H_{14}N_2$	198.26
Ascorbic acid	54670067	$C_6H_8O_6$	176.12

Molecular docking

Docking studies yielded crucial information concerning the orientation of ligand in the binding pocket of the target protein. Each compound was docked against the structure of $A\beta_{42}$ monomer in both polar (hereafter referred as 1IYT receptor) and apolar (hereafter referred to as 1Z0Q receptor) to determine their binding affinity using AutoDock Vina [Trott, Haas, 2007). The grid and docking parameter files were prepared using AutoDock Tools (ADT) [7]. The grid boxes with dimensions of 126 x 74 x 126 Å with grid spacing 0.403 Å and 126 x 82 x 76 Å with grid spacing 0.419 Å were defined for 1IYT and 1Z0Q respectively. These customized dimensions are large enough to cover the whole protein and leave enough space for ligands to be docked on surface.

The two-dimensional graphical depictions of best docked complexes were accessed using Ligplot+v.1.4.5 [Wallace,1995, Laskowski,2011, 8] and detailed analysis on the physicochemical of the docked complexes were obtained from PLIP: fully automated protein–ligand interaction profiler [9].

Results and Discussion

Molecular docking has been used to predict most stable conformation of a non-covalently bound molecule towards the other one as well as its binding afinity. Binding afinity is the strength of the binding interaction between a single biomolecule to its ligand, which used to estimate and rank order strengths of biomolecular interactions. It is influenced by non-covalent intermolecular interaction such as hydrogen bonding, hydrophobic, electrostatic intercations and van der Waals forces between the two molecules.

In this study, AutoDock Vina was utilised to estimate the mode corresponds to the binding afinity between the ligands and proteins. The binding afinity predictibility of AutoDock Vina was corelated with the experimental binding afinity coresponded with non-specific van der Waals and hydrophobic interaction scores between ligands and receptors [10].

The binding afinity obtained in the best mode are shown in TABLE II. Folic acid (MW=441.40 g/mole) and Donepezil (MW=379.49 g/mole) show high binding afinity to $A\beta_{42}$ monomer in both polar and apolar environment, in comparison to the other ligands. The weakest binding afinity was observed for ascorbic acid (MW=176.12 g/mole). The protein-ligand binding energy tend to correlate with the molecular weight of the ligands to some extent.

TABLE II. BINDING AFINITY OF ANTI-ALZHEIMER COMPOUNDS WITH 1IYT AND 1Z0Q RECEPTORS

Ligand name	Targeted $A\beta_{42}$ Peptides	Binding Afinity (kcal/mol)
Curcumin	1IYT	-4.5
	1Z0Q	-5.1
Donepezil	1IYT	-5.2
	1Z0Q	-6.3
Folic Acid	1IYT	-5.6
	1Z0Q	-6.0
Galantamine	1IYT	-5.4
	1Z0Q	-5.3
Ibuprofen	1IYT	-4.7
	1Z0Q	-4.5
Rosmarinic acid	1IYT	-4.3
	1Z0Q	-5.5
Rivastigmine	1IYT	-4.0
	1Z0Q	-4.3
Tacrine	1IYT	-5.1
	1Z0Q	-5.7
Ascorbic acid	1IYT	-3.8
	1Z0Q	-3.9

Molecular docking studies were done to investigate the interaction of anti-Alzheimer's molecules with $A\beta_{42}$. TABLE III shows the hydrogen bonding, hydrophobic and π-stacking interactions of the docked complexes. Folic acid forms favorable hydrogen bonding and hydrophobic interaction with both 1IYT and 1Z0Q receptors. Surprisingly, the hydrogen bond, hydrophobic and π-stacking interactions exist between folic acid compound and $A\beta_{42}$ peptide in apolar environment. Three types of interactions such as hydrogen bonds, hydrophobic and π-stacking exist between donepezil and $A\beta_{42}$ receptors.

TABLE III. THE NUMBER OF HYDROGEN BONDING, HYDROPHIC AND π-STACKING FORMED IN PROTEIN-LIGANDS INTERACTIONS

Ligand name	Targeted $A\beta_{42}$ Peptide	H-bond	Hydrophobic	π-Stacking
Curcumin	1IYT	2	4	1
	1Z0Q	3	4	1
Donepezil	1IYT	1	3	1
	1Z0Q	1	2	1
Folic Acid	1IYT	5	3	1
	1Z0Q	8	2	0

Galantamine	1IYT 1Z0Q	1 3	3 2	0 0
Ibuprofen	1IYT 1Z0Q	1 0	3 4	1 0
Rosmarinic acid	1IYT 1Z0Q	1 1	3 2	1 1
Rivastigmine	1IYT 1Z0Q	0 1	3 2	1 1
Tacrine	1IYT 1Z0Q	2 2	3 4	1 0
Ascorbic acid	1IYT 1Z0Q	3 5	0 0	0 0

Hydrogen bond interactions are crucial to ligand protein binding. Folic acid showed the highest interaction by forming two hydrogen bonds with Glu3 and Gly9, and one hydrogen bond between His13 residues of 1IYT receptor. In 1Z0Q receptor, it forms eight hydrogen bonds; two hydrogen bonds with Glu11, Gln15 and Asn27, and one hydrogen bond with Glu22, and Asp23. A hydrogen bond exists against donepezil with Gln15 residue in both 1IYT and 1Z0Q receptors.

As shown in Fig. 1, one hydrogen bond was observed between the NH group on the quinazoline ring, and the other NH group of the folic acid with the carboxyl groups of Glu3 at distance of 2.97 Å and 3.69 Å, respectively. The third and fourth hydrogen bonds were observed between NH and carboxyl groups of folic acid with the carboxyl groups of Gly9 at distance of 3.17 Å and 2.99 Å, respectively. In addition, folic acid forms one hydrogen bond between NH with the carboxyl group of His13 at distance of 3.89 Å.

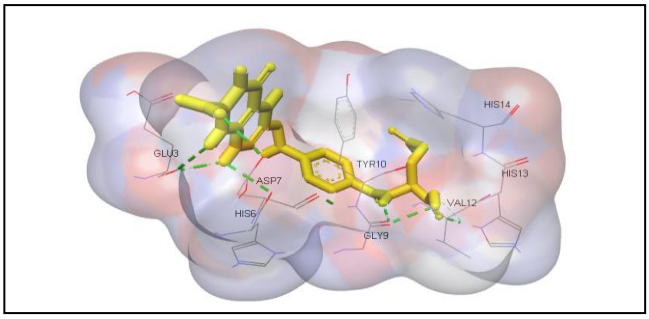

Fig. 1. *3D structure of folic acid docked to 1IYT receptor*

Donepezil interact via hydrogen bond through its NH of amine group with Gln15 at distance 3.76 Å (Fig. 2).

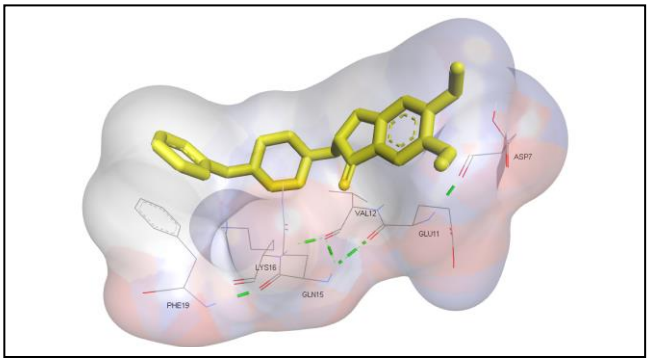

Fig. 2. *3D structure of donepezil docked to 1IYT receptor*

Folic acid has some hydrophobic interaction with two amino acids of His6 and Thr10 against 1IYT receptor; the His6 forms one hydrophobic interaction at distance 3.85 Å and Thr10 forms two hydrophobic interactions at distance 3.68 Å and 3.66 Å, respectively. In addition, folic acid interacts via π-stacking bonds with Try10.

Donepezil interacts via π-stacking bond with Phe19 and some hydrophobic interactions; the Glu11 forms one hydrophobic interaction at distance 3.74 Å and Val12 forms two hydrophobic interactions at distance 3.93 Å and 3.46 Å, respectively (TABLE III).

In 1Z0Q receptor, folic acid interact via hydrogen bonds through its NH group on the quinazoline ring and the other NH group of the folic acid with carboxyl groups of Glu11 at distance 3.17 Å and 2.86 Å, respectively. The two hydrogen bonds exist between NH of folic acid moiety with the NH_2 groups of Gln15 at distance 3.76 Å and 3.64 Å, respectively. The other NH and carbonyl groups of folic acid form hydrogen bonds between the carbonyl groups of Asn27 at distance 3.02 Å and 3.79 Å, respectively. In 1Z0Q docked complex, carboxyl group of folic acid interact by hydrogen bond with Glu22, and Asp23 at a distance of 3.05 Å and 3.06 Å, respectively (Fig. 3).

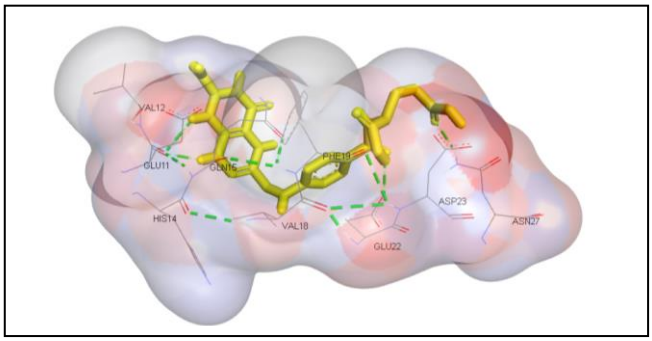

Fig. 3. *3D structure of folic acid docked to 1IYT receptor*

As shown in Fig. 3, one hydrogen bond was observed between the NH amine of donepezil with Gln15 at distance of 3.10 Å in 1IZ0Q docked complex.

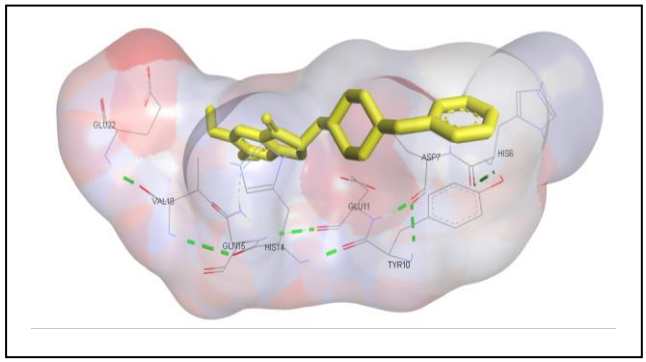

Fig. 4. *3D structure of denopezil docked to 1Z0Q receptor*

In 1Z0Q receptor, folic acid has two hydrophobic interactions with two hydrophobic amino acids of Val18 and Glu22 at distance 3.98 Å and 3.68 Å, respectively. Donepezil interacts via two hydrophobic interactions with Glu11 and Val18 at distance 3.79 Å and 3.65 Å, respectively. There is also a π-stacking bond with Tyr10 residue of 1Z0Q receptor.

Folic acid is one of the B-complex vitamins with an aromatic compounds contains two carboxyl groups and one aryl ring join to a dihydropteridine ring. Based on our result, it's highly interacting with Glu11, Glu22, Phe19 and Asp23 in both 1IYT and 1Z0Q receptors. This suggests a possible amyloid inhibitory mechanism of folic acid compound by binding and masking amyloidogenic region in the peptide, thus preventing self-aggregation of Aβ peptide. Furthermore, the essential role of hydrogen bonding and hydrophobic interaction assist the binding of folic acid towards Aβ peptide, which might prevent further elongation of the Aβ fibrils.

Conclusion

Alzheimer is the most common forms of dementia characterized by deposition of Aβ peptide. Several natural compounds have been used to improve memory and cognition in AD patients as supported by various experimental studies. Docking study that was applied to analyse the best docked ligands permitted us to know the binding mode of compounds to the target Alzheimer peptides. The amino acids that contribute the most to the interaction of folic acid and donepezil compounds with active site of Aβ protein model are Glu11 and Phe19, followed by Gln15, Glu 22 and Val12. This study found that folic acid has strong interactions with Aβ peptide by forming more hydrogen bonds, hydrophobic as well as π-stacking interactions with both 1IYT and 1Z0Q receptors. The findings from this study might assist researchers in designing Aβ inhibitors and formulate folic acid supplement as a treatment for AD.

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