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DRUG DISCOVERY

Virtual Screening Analysis for Drug Designing against Precursor Protein of Alzheimer's disease

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ABSTRACT

Alzheimer's disease is a neurodegenerative disorder. In this type of disease there is loss of structures or the function of neurons,in which Amyloid plaques are formed by aggregation of Aβpeptide. Aβpeptides are generated by successive cleavages of amyloid precursor protein (APP) by βand γsecretase enzyme.In recent years, several approaches aimed at inhibiting disease progression have advanced to clinical trials. Therefore we have taken the Alzheimer's amyloid beta-protein cause for the disease.To inhibit the activity of this protein we have taken many inhibitory molecules from the various sources and analyze binding interaction to target protein on the basis of docking energy and after this, predict the effects of therapeutic molecules on human body. There is substantial in-silico data indicating that therapeutic molecules have antioxidant, anti-inflammatory, and anti-amyloid activity.

Keywords: Alzheimer disease; βamyloid; APP; Inhibitory molecules; Docking; virtual screening.

Abbreviation: AD – Alzheimer disease; APP – Amyloid precursor protein.

1. INTRODUCTION

Alzheimer's disease (AD) the most common form of irreversible dementia. It is a progressive neurodegenerative disease that gradually destroys brain function or neuron function. Primarily affects the elderly population, and is estimated to account for 50-60% of dementia cases in persons over 65 years of age.Disease imposes financial burden on family and society. Current line of treatment only provides symptomatic relief (Davis & Powchik 1995; Sugimoto et al., 1995). Its pathological Symptoms include forgetfulness and memory loss (Mattson, 2004). This disease is characterized by production of amyloid beta (Aβ) plaques; Amyloid plaques are formed by aggregation of Aβ peptide (Glenner & Wong, 1984).

42 amino acid form of Aβhas been identified as the predominant constituent of plaques (Yin et al., 2007). Aβpeptides are generated by successive cleavages of amyloid precursor protein (APP) by β and γsecretase (Potter & Dressal, 2000) enzyme. Aβcan also be cleaved by αsecretase enzyme. Aβ42 is produced by cleavages taking place in Golgi (Hartman et al., 1997) apparatus. No one knows for certain what causes Alzheimer's disease (AD). Many factors are involved, including inflammation, oxidative damage, and cytoskeletal abnormalities. For prevention of Alzheimer disease many hypothesesare comes out such as Amyloid hypothesis, cholinergic hypothesis etc.

1.1. Amyloid hypothesis

According to the amyloid hypothesis, accumulation of Aβ in the brain is the primary influence driving AD pathogenesis. In which Amyloid β precursor protein cleavage by the β secretase and endoproteolyzed by γ secretase to yield the $A\beta_{42}$ monomer unit, accumulation of $A\beta_{42}$ monomer isoform form toxic Aβ 1-42 oligomer and deposit in the form of Aβ plaques. These plaques are causes of aberrant signals in signal transduction process which lead to the cell death eventually and arise Alzheimer's symptoms.Therefore preventive and curative strategies deal with reduction in Aβ42 production. Hence we have taken Alzheimer's amyloid beta-protein precursor (AAP1) as a target that cause for the disease. Alzheimer's amyloid beta-protein precursor contains a Kunitz protease inhibitor domain (APPI) potentially involved in proteolytic events leading to cerebral amyloid deposition.To facilitate the identification of the physiological target of the inhibitor. Nowadays the treatment only provides symptomatic relief (Davis & Powchik 1995; Sugimoto et al., 1995). Commonly used drugs are Acetylcholine esterase inhibitors (Sugimoto et al., 1995) which temporarily alleviate symptoms by raising levels of neurotransmitter Acetylcholine and thus improving cognitive behavior. Computer aided drug designing uses computational principle to discover or to study drugs and biologically active molecules.

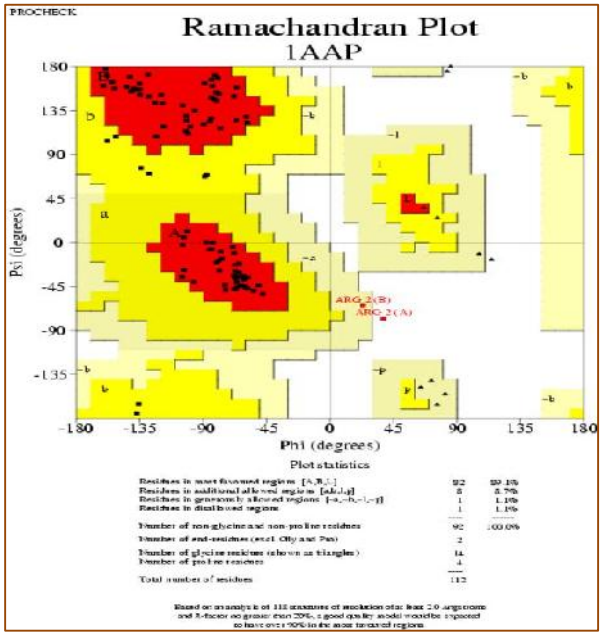

Figure 1

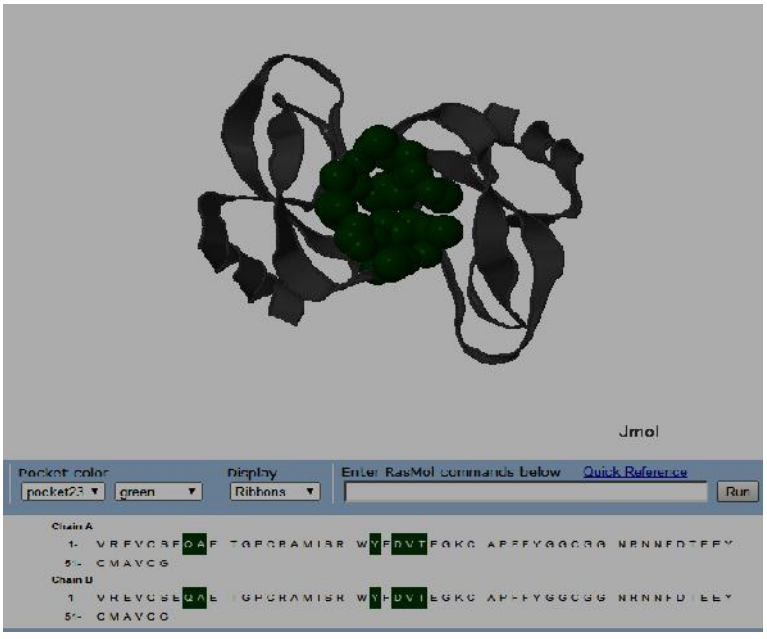

Figure 2

2. EXPERIMENTAL PROCEDURE

We identify the target that cause for Alzheimer disease, several research papers and literature use for to extract the knowledge to identify the target. This step involve in target identification process in drug designing, after the target identification, we takethe "X-ray crystal structure of the protease inhibitor domain of Alzheimer's Amyloid beta-

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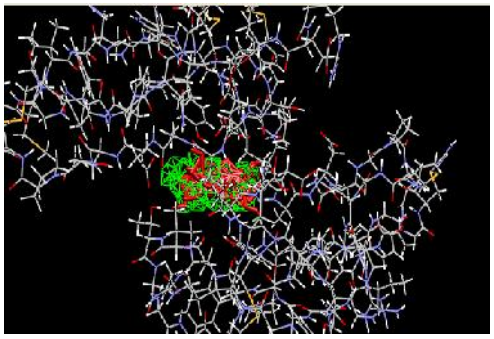

Figure 3

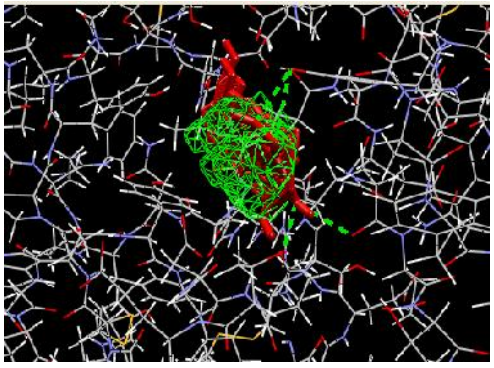

Figure 4

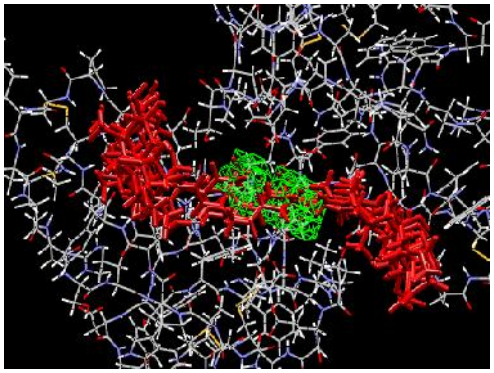

Figure 5

protein precursor" and its PDB id is 1APP as a target from the protein data bank database and analyze the structure of the target through the protein visualization software Rasmol, which predict the polar, nonpolar, helices, sheets region and hydrogen bonds etc.in the structure. After that we validate the target through the prochek software that draw the ramachandran plot (Figure 1), which show the allowed, favorable, and disallowed regions between the ϕ and ψ angles, and this process involve in target validation process of drug designing. For targeting the Alzheimer disease we take at least fifteen inhibitory molecules that show anti-alzheimeric activity. These all fifteen molecules taken from the several sources such as herbal, aquatic, medicinal plants and many organic compounds and prefer many research papers that help in identify the inhibitory molecules. These all inhibitory molecule's structure taken from the various databases such as pubchem, drugbank, and chemspider, some molecule's structure are not available in these databases, that inhibitory molecule's ware drawn by using the software Marvin.

Thus we have all structures of the fifteen molecules. Before the docking between target and lead molecules, we predict the active site prediction in the target protein with the aid of castp and Q-sitefinder (Figure 2). Ligand binding site prediction is necessary for docking because true ligand-binding site would exhibit stronger affinity to the compounds in the random library than the other sites, even if the random library did not include the ligand corresponding to the true binding site. We also assumed that the affinity of the true ligand-binding site would be correlated to the docking scores of the compounds in the random library.

After ligand binding site prediction, begins the docking between target protein and inhibitory molecules, with dock all possible orientations of a ligand and its receptor can be generated. Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using for example scoring functions. Hence in which we dock fifteen molecules to target protein in molegro virtual docker software and analyze the binding affinity on the bases of scoring function.

2.1. Molecules property prediction

After analyzing the dock score, we analyze the effectsof the inhibitory molecules on human health, through the molecular property explorer which available on http://www.organic-chemistry.org/prog/peo/. In which Prediction results are valued and color coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a greencolor indicates drug-conform behavior.

3. RESULTS

The observation of docking between inhibitory molecules and target protein shows that all inhibitory molecules form stable complex with target protein which indicate dockenergy, some dock score and molecules are given below which form a stable complex. After dock score we analyze the different effects of molecules, the result of molecular property explorer shows that only seven molecules are not harmful for humans and two molecules are neutral which are nor toxic and neither drug likeness, rest are show the undesired effects on human body, some are given below.

3.1. Best Dock Results

1. (+)-Catechin (Figure 3)

2. Myricentin (Figure 4)

3. Fucoxanthin (Figure 5)

3.2 Dock Score of Inhibitory Molecules

(Table 1)

Table 1

S.No.	Inhibitory molecules	Target protein	Dock Score
1	(+)-catechin	Alzheimer's Amyloid β protein precursor	-147.922
2	Myricetin	Alzheimer's Amyloid β protein precursor	-146.744
3	Fucoxanthin	Alzheimer's Amyloid β protein precursor	-140.538
4	Nimodipine	Alzheimer's Amyloid β protein precursor	-135.416
5	Rosmarinic acid	Alzheimer's Amyloid β protein precursor	-131.626
6	Loganin	Alzheimer's Amyloid β protein precursor	-119.574
7	HU-210	Alzheimer's Amyloid β protein precursor	-118.529
8	Physostigmineheptyl	Alzheimer's Amyloid β protein precursor	-130.665
9	Naringin	Alzheimer's Amyloid β protein precursor	-129.995
10	Hesperidin	Alzheimer's Amyloid β protein precursor	-124.215
11	Peseudobaptisin	Alzheimer's Amyloid β protein precursor	-157.087
12	Reserprine	Alzheimer's Amyloid β protein precursor	-139.085
13	Vaganine D	Alzheimer's Amyloid β protein precursor	-126.79
14	Ginkgolide B	Alzheimer's Amyloid β protein precursor	-137.141
15	Curcumim	Alzheimer's Amyloid β protein precursor	-133.633

4. DISCUSSION

From the dock result Catechin has the highest binding energy in all fifteen molecules, which indicate strongest stability when dock with the target protein, in molecular property prediction catechin show highly drug likeness property and nontoxic for humans. With the analysis of dock result Myricentin also indicate the highest binding affinity, its molecular formula is $C_{15}H_{10}O_8$ and in molecular property prediction it show the highly mutagenic and medium risk tumorigenic and reproductive effective, and the third inhibitory molecule is Fucoxanthin it also has the strong binding affinity with target protein and its molecular formula is $C_{42}H_{58}O_6$ and Fucoxanthin show the medium risk mutagenic property. Thus in top three inhibitory molecules out of fifteen molecules, Catechin only show the highest binding affinity and highly drug likeness property.

5. CONCLUSION

This analysis reveals that Amyloid β cleavage by the β secretase and endoproteolyzed by γ secretase to yield the $A\beta_{42}$ monomer unit, accumulation of $A\beta_{42}$ monomer isoform form toxic Aβ 1-42 oligomer and deposit in the form of Aβ plaques. To inhibit the activity of amyloid β we take fifteen molecules which show different dock score on target protein with the aid of docking program and after this we describe the properties of the molecules, only seven molecules, (+)-catechin, rosmarinic acid, Vaganine, and Ginkgolide- J55show the best result in Drug likenesspreidiction through molecular property explorer.

SUMMARY OF RESEARCH

1. Alzheimer's disease is a neurodegenerative disorder. In which Amyloid plaques are formed by aggregation of Aβpeptide.
2. Aβpeptides are generated by successive cleavages of amyloid precursor protein (APP) by βand γsecretase enzyme. Therefore we have taken the Alzheimer's amyloid beta-protein cause for the disease.
3. To inhibit the activity of this protein we have taken many inhibitory molecules from the various sources. These inhibitory molecules interact with the target protein and indicate the various binding energy, the highest binding energy in negative, shows the highest satability with target protein,
4. After analyzing the dock energy we predict the molecular property of the inhibitory molecules. In which we analyze the toxicity of the molecules for human health.

FUTURE ISSUSE

Currently available treatments for AD are symptomatic and do not prevent the progression of the disease. The development of drugs for AD is recognized as a worldwide necessity. These must presumably be drugs that will prevent, the molecular pathological steps leading to neurodegeneration and finally dementia.

DISCLOSURE STATEMENT

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