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Biocomputational Approach for the Effective Treatment of Alzheimer's Disease

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Abstract

Objective: Alzheimer's disease is age associated cognitive brain disorder. It is irreversible progressive neurodegenerative disease where in the neurons get degenerated as the time passes by. Amyloid Precursor Protein takes a central position in causing the disease. The main objective of our studies is to inhibit the BACE1 protein. **Methods:** Computational biology and bioinformatics not only speed up the research but also reduce the cost thus playing a very crucial role in health care domains to treat various diseases. For current studies 108 Phytochemicals were retrieved from PubChem. Drug-likeness of these phytochemicals was evaluated by using Lipinski's rule of five. Out of 108 only 27 Phytochemicals were able to satisfy Lipinski's rule and Blood Brain Barrier. These 27 potential phytochemicals were taken for Docking studies. The BACE1 (5HU1) protein was retrieved from PDB. Molecular Docking was performed using PyRx software. **Results:** Docking results were evaluated by analyzing the binding affinities (kcal/mol). Myrcenyl acetate had the lowest binding affinity while Sakuranetin had the highest binding affinity. **Conclusion:** Our current studies have focused on Phytochemicals as they have anti-amyloidogenic, anti-cholinergic, anti-inflammatory, Antioxidant and anti-microbial properties. They are known to inhibit the amyloid accumulation. Phytochemicals included Flavones, Flavonols, Isoflavones, Flavanols, acids, Esters and phenolic compounds. Due to speed in research and cost effectiveness, the Insilico approaches have acquired a central place in drug discovery. In our insilico study phytochemicals are taken and fit in receptor molecule (BACE1) in 3D space. PyRx, a virtual screening tool is used for docking wherein all the 3D structures of Phytochemicals such as Resveratrol, Galantamine, Berberin etc. have been docked with BACE1. Sakuranetin has the highest negative value obtained from our docking calculations. Thus, seeming to prove more effective in the treatment of Alzheimer's disease.

Keywords
Alzheimer's Disease, Neurodegenerative disorder, Phytochemicals, beta amyloid, Molecular docking

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INTRODUCTION:

Alzheimer's Disease is a progressive neurodegenerative disease. It is the 6th most leading cause of death in the world. It is abbreviated as AD. It is most common type among other forms of dementia afflicting about 10% of the population over the age of 65 and about 50% of the population over the age of 85[1]. King's College London has documented The World Alzheimer Report 2015 says that 46.8 million people are currently living with dementia[2]. In future, 74.7 Million by 2030 and 131.5 Million by 2050 around the world. According to 2015 statistics, 4.1 Million people are having dementia in India alone[4]. AD is the most common dementia accounting for roughly half of all cases.[3].

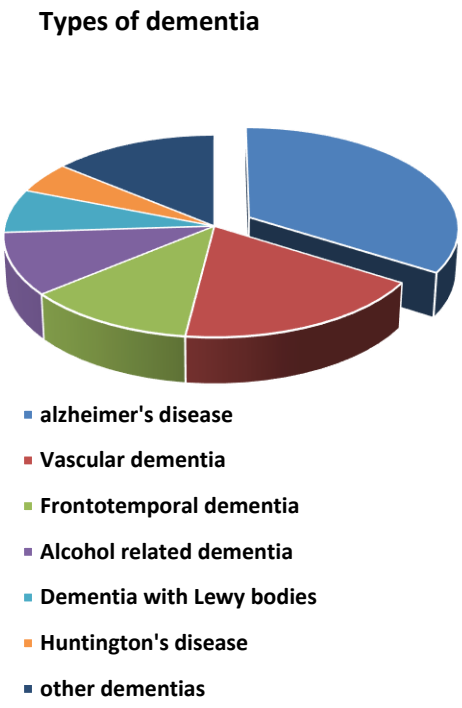

Fig 1: Reference: Harvey RJ, Skelton-Robinson M, Rossor MN, *et al*. The prevalence and causes of dementia in people under the age of 65 years. J Neurol Neurosurg Psychiatry 2003; 74:1206–9.

A German Neuropathologist and psychiatrist named Dr. Alois Alzheimer is known to be attributed for the Alzheimer's Disease[4]. It affects mainly females than males, at the age of 60 and above. In 1906 Alzheimer's came into light when patient named Auguste had a peculiar dementing condition. During autopsy Dr. Alzheimer's noticed senile plaques and neurofibrillary tangles NFTs which lead to aggregation of beta amyloid protein both extracellular and intracellular[5]. The presence of toxic tau proteins and beta amyloid proteins activate the immune system cells present in the brain known as microglia. Microglia plays an important role in clearing the toxic proteins[6]. APP takes a central position in AD. It is trans-membrane protein; it is normally cleaved by alpha secretase at the amino terminus and gamma secretase at the carboxyl terminus to form soluble beta amyloid. When the APP is cleaved by beta secretase and gamma secretase at the amino and carboxyl terminus respectively, insoluble amyloid peptides are generated. The beta amyloid consists of multimeric aggregates of peptides of about 40 to 42 amino acid peptides[7,8]. These insoluble peptides accumulate in the hippocampal region of the brain leading to deterioration of cognitive function[9]. AD can be early onset or late onset[5]. The early onset maybe related to inherited genetic mutations[10] known as FAD (Familial Alzheimer's Disease), accounts for 5% of all cases. The late onset is age associated decline of cognitive function[10] which usually occurs after the age of 60, accounts for 95% of all cases[11, 12]. Though the etiology behind AD is not known, But there is proof that suggests the accumulation of senile plaques and NFTs[13] to be responsible for this cognitive disorder. This results in synaptic dysfunction, disrupting the communication[14] with neural circuits which are important for memory and cognitive functions[15].

The role of Computational Biology and Bioinformatics has become important nowadays. The screening of medicinal plants to find their effectiveness to a disease is done through in silico approach[16]. Molecular docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to a stable complex[17, 18]. In current studies PyRx[19] is being used to calculate the binding energies.

Phytochemical studies reveal the presence of various valuable compounds such as lignans, flavonoids, sterols, alkaloids, triterpenes, polyphenols and tannins. These show wide variety of pharmacological activities such as anti-inflammatory, anti-amyloid, anti-cholinergic, antioxidant and hypolipedemic[20].

MATERIALS AND METHODS:

Protein Preparation:

The Three-dimensional (3D) structure of the BACE1 was retrieved from Protein Data Bank in PDB format. The PDB ID is 5HU1(shown in figure 6). The 3D structure of 5HU1 was retrieved

The 3D structure of protein was visualized in Discovery Studio and water molecules present in the protein were deleted.

Fig 2: 3D structure of BACE1

Active site prediction:

Followed by the removal of water, the ligand was selected to determine the binding sites in Discovery studio. The active sites predicted were Try32, Gly72, Gln73, Leu91, Asp93, Ser96, Gly95, Tyr132, Phe169, Ile171, Trp176, Asp289, Thr292, Thr293 and Ala396.

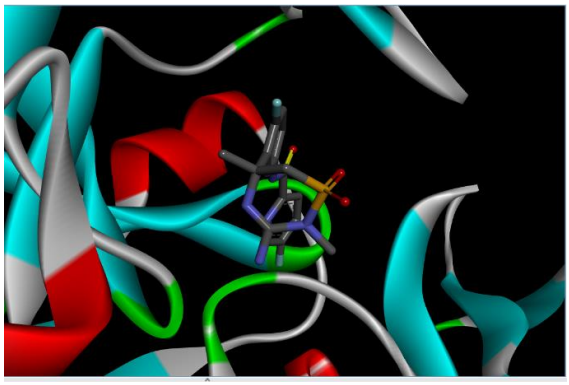

Fig 3: Visualization of ligand in protein.

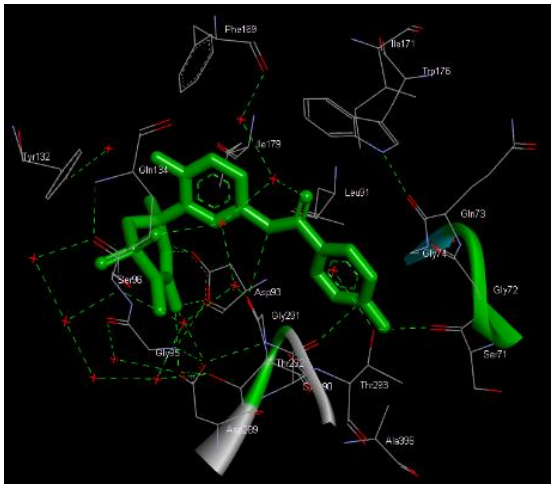

Fig 4: Shows the Active site amino acid residues.

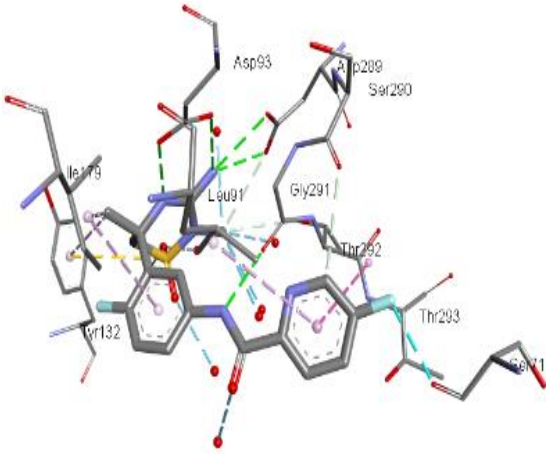

Fig 5: Shows the Active site amino acid residues.

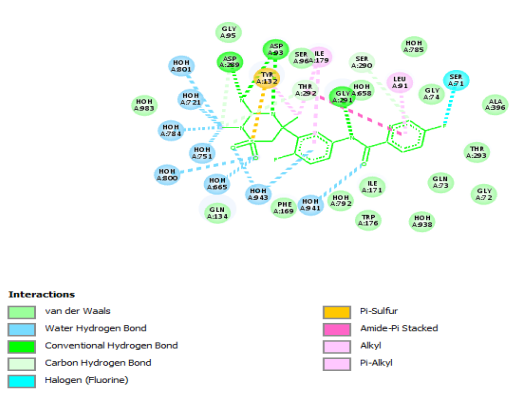

Fig 6: shows the 2D representation of ligand interaction.

Preparation of ligand:

PubChem is an Open Chemistry Database at the National Institutes of Health (NIH). The 3-Dimensional structures of Phytochemicals were available at PubChem in SDF format. The file conversion from SDF to PDB becomes necessary as the docking software demands it. The conversion of file formats was carried out using SMILES online converter to convert SDJ to PDB file format.

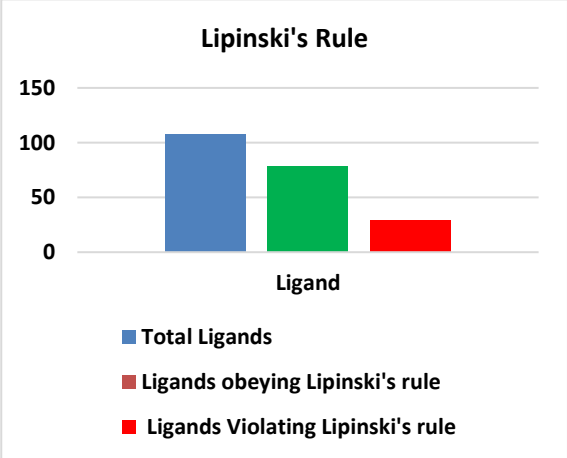

Fig 7: Graphical representation of ligands based on Lipinski's rule.

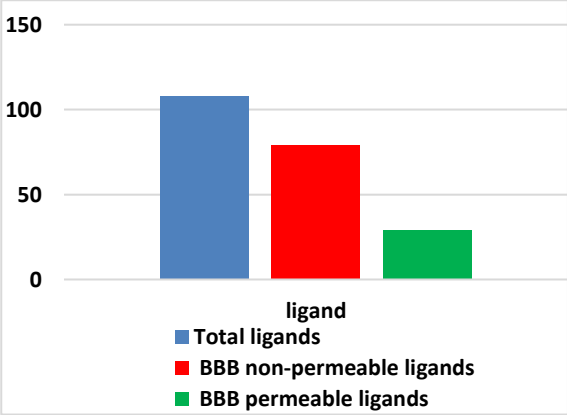

Fig 8: Graphical representation of ligands based on BBB.

Molecular Docking Studies:

The Molecular docking of 27 ligands with BACE1 protein was carried by using PyRx, a virtual screening tool. A grid box was set at the active sites then phytochemical was imported into the software. The binding energies of phytochemicals with BACE1 were noted down.

RESULTS:

Table 1: The ligands with their respective binding affinities (kcal/mol).

Sl No	Ligand	Binding Affinity (kcal/mol)
1.	Resveratol	-7.1
2.	Berberin	-7.9
3.	Galantamine	-7.6
4.	Terpenoids (Myrcenyl acetate)	-5
5.	HuperzineA (Fordine)	-7.7
6.	Nicotine	-5.8
7.	Physostigmine	-7.7
8.	Chrysin	-7.6
9.	Isosakuranetin	-7.7
10.	Pinocembrin	-7.6
11.	Sakuranetin	-8.0
12.	Harmolol	-6.7
13.	Harmane	-6.5
14.	Harmine	-6.8
15.	Harmol	-7.0
16.	Harmaline	-6.9
17.	Cinnamic acid	-6.4
18.	Melatonin	-6.9
19.	Onysilin	-7.9
20.	Scopoletin	-6
21.	Carvacrol	-6.4
22.	Eugenol	-5.7
23.	Thymol	-5.9
24.	Daidzein	-7.7
25.	Pterostilbene	-7.1
26.	Salicyclic acid	-5.4
27.	Tangeritin	-7.1

The current study helps in understanding the interaction between the ligands and BACE1 protein and explore the binding affinity between them. The docking studies were performed using PyRx virtual screening tool. The drug-likeness is checked by screening of compounds through the lipinski's rule of five and ADMET is usually done to avoid the failure rate of the of the drug in the future. Out of 108 ligands only 27 had satisfied the Lipinski's rule of five and ADMET properties. These 27 ligands were considered for molecular docking. BACE1 was docked with all 27 ligands. The ligand showing higher negative value is the most efficient in the treatment of AD. The binding affinity ranges from -5 kcal/mol to -8 kcal/mol. Myrcenyl acetate had the lowest binding affinity while Sakuranetin had the highest binding affinity. Thus, Sakuranetin is the most efficient among the other ligands used for molecular docking.

DISCUSSION:

The etiology behind Alzheimer's disease is not known but studies have shown Amyloid, Tau and Cholinergic hypothesis to be the reason. However, APP takes up the central position in causing AD. Some studies have shown some drugs as Cholinergic and amyloidogenic inhibitors. When Beta secretase is mutated it results in the accumulation of beta amyloid in the hippocampal region of the brain. Our current insilico studies use phytochemicals to inhibit the beta secretase (BACE1). Phytochemicals play an incredibly significant role as they have potential to boost immune system. The phytochemicals are used as a

brain booster in Ayurveda medicine due to their efficiency and potentiality. They possess Anti-Inflammatory, Anti-Tumorigenic, Anti-Amyloidogenic, Anti-Cholinergic, Antioxidant, Anti-Microbial and Chemotherapeutic properties. Because of their crucial properties they provide protection against wide variety of diseases such as Diabetes, Cancer, Heart diseases, Cataract and Neurological diseases. Because of such reasons the phytochemicals have gained a lot of attention from the pharmaceutical companies. Although phytochemicals have great potential for treating neurological disorders but face a very big challenge to make their way through the Blood Brain Barrier. Mainly for the CNS related diseases BBB is of prime importance because the phytochemicals have to permeate itself through this barrier. They are promising potential drugs that could treat the neurological disorders. The insilico studies have saved time and money through screening of the drugs. Some studies have been taken from insilico to in vivo and invitro to analyze and compare both the studies. In our present insilico studies 106 phytochemicals have been considered. The phytochemicals which are having good pharmacokinetic properties have been selected and taken for further future studies. The studies so far carried out have used curcumin and its derivatives, flavonoids from gingko biloba (Yellamma et al 2016, Ashish Kumar et al). While in our study there is combination of all these as we have used all the phytochemicals listed in the Literature. The Lipinski's filters were used to check the drug-likeness of the compound. Around 78 compounds showed drug-likeness. While the BBB was also checked to ensure if the drug is permeable through the blood. Only 27 compounds were able to pass through the BBB. The compounds which were able to pass through both criteria to satisfy drugs were only 27 compounds. These compounds have shown the binding affinities ranging from 5 kcal/mol to 8 kcal/mol. The binding affinities vary from studies carried by other individuals depending upon the type of software employed by them. Sakauratin has the higher negative value and seem to have good potential in treating the Alzheimer's disease. The importance of phytochemicals has been realized and it may have long run. Biocomputational studies have gained lot of importance in the pharmaceutical world.

CONCLUSION:

Alzheimer's is the sixth most leading cause of death. It is noticed as per 2015, 46.8 million people are currently living with dementia[4]. In future, 74.7 Million by 2030 and 131.5 Million by 2050 around the world. In 2015, India alone had about 4.1 million people suffering from dementia. Till date there is no cure for Alzheimer's disease. The medicines prescribed are known to slowdown it's neurodegeneration. Nowadays Donepezil, Namenda etc. have been used. Our current studies have focused on Phytochemicals as they have anti-amyloidogenic, anti-cholinergic, anti-inflammatory, antioxidant and anti-microbial properties. They are known to inhibit the amyloid accumulation. Phytochemicals included Flavones, Flavonols, Isoflavones, Flavanols, acids, esters, phenolic compounds. Computational biology and bioinformatics have great potential to speed up research work and help in reducing the cost. Docking is a method in which a drug molecule is docked with receptor molecule. It is a process by which two molecules fit together in 3-Dimensional space. Due to speed in research and cost effectiveness, the Insilico approaches have acquired a central place in drug discovery. In our insilico study phytochemicals are taken and fit in receptor molecule (BACE1) in 3D space. PyRx, a virtual screening tool is used for docking wherein all the 3D structures of Phytochemicals such as Resveratrol, Galantamine, Berberin etc. have been docked with BACE1. Sakuranetin has the highest negative value obtained from docking calculations. Thus, seeming to prove more effective in the treatment of Alzheimer's disease.

CONFLICT OF INTEREST:

The authors report no conflicts of interests in this work.

AUTHOR'S CONTRIBUTION:

All authors conceived and designed the study. All the authors have engaged in conducting the experiments, analyzed the data and wrote the paper. All authors have contributed to manuscript revisions. All authors have read and approved the final version of the manuscript.

AUTHOR FUNDING:

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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