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In silico Identification of novel ApoE4 inhibitor for Alzheimers disease therapy

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ApoE4 is a major genetic risk factor due to its increase incidence of developing Alzheimer???s disease. The study was designed to predict such compounds that may helpful in designing drug to suppress the over activity of apoE4 protein. 22 natural compounds (marine, microorganism and plant derivative) were used as inhibitors and docked with apoE4 (PDB id 1B68). 6 Synthetic compounds (In clinical trials) were docked with target protein to compare and analyze the docking results with natural compounds. Compounds S-Allyl-L-Cysteine, Epicatechin Gallate and Fulvic Acid show high binding affinity i.e. -7.1, - 7 and -7 respectively. Epicatechin Gallate shows hydrogen bond with Gln156 and Asp35 and Fulvic Acid shows hydrogen bonding with Glu27. In case of synthetic compounds Tideglusib did not show hydrogen bonding with any amino acid residue of ApoE4 but show high binding affinity of -7.2 same as of natural compound S-Allyl-L-Cysteine which show high binding affinity of -7.1 but did not show hydrogen bonding with any amino acid residue. Protein-Protein interactions of apoE4 show physical and functional interaction with related proteins. Our study predict a compound Epicatechin Gallate on the basis of binding affinity and hydrogen bonding with amino acid residue as a potential lead compound which may be used as an inhibitor.

Alzheimer's disease (AD) is one of the most common causes of dementia in the society. AD is generally classified into two types: (1) early onset/familial AD (FAD); and (2) sporadic AD (SAD). The malfunctioning and gradual death of neurons in the disease results in loss of memory and cognitive functions. The disease is characterized by accelerated accumulation of amyloid β (Aβ) plaque around neurons and hyperphosphorylated microtubule associated tau protein in the form of neurofibrillary tangles within the cells. The degradation of hyperphosphorylated tau by the proteasome system is also inhibited by the actions of Aβ. Amyloidogenic pathway results from a mutation and replaces the normal pathway in which α-secretase acts on the amyloid precursor protein (APP), a membrane protein, followed by γ-secretase forming a harmless peptide but the amyloidogenic pathway involves the breakdown of APP by β-secretase followed by γ-secretase, and results in the formation of Aβ plaque, whose major constituent is the 42 residue long Aβ42. AD is a progressive neurodegenerative disorder characterized by progressive loss of memory, declining cognitive function, decreased physical function, and ultimately the patient's death due to the death of the brain cells The progression of AD can be broken into three basic stages: (1) preclinical (no signs or symptoms); (2) mild cognitive impairment; and (3) dementia. Recent reports suggest that > 4.7 million people of ≥ 65 years of age are living with AD in the USA.8AD is predicted to affect one in 85 people globally by 2050.

Aβ oligomers and plaques are potent synaptotoxins, block proteasome function, inhibit mitochondrial activity, alter intracellular Ca2+ levels, and stimulate inflammatory processes. The above processes contribute to neuronal dysfunction. Hyperphosphorylation of tau protein leads to the accumulation of neurofibrillary tangles within the neurons. As a result the biochemical and synaptic communication between neurons is disrupted which results in the gradual death of the cells. The majority of the cases of AD are SAD. FAD is caused by autosomal dominant mutations in either APP or the presenilin-1 or -2 gene/protein. A gene known as the Apo-ε4 is one of the factors associated with higher chances of sporadic AD. The risk factors for SAD include aging leading to a gradual deterioration of function, presence of the apolipoprotein E4 (APOE4) allele, and vascular diseases such as stroke and cardiac disease.

Computer-aided drug design or computational drug discovery has been one of the major tools applied in drug discovery programs used to reduce the cost and process time. The major parts of computer-aided drug design are structure based drug design, ligand based drug design, and sequence based approaches. The most widely used chain for drug discovery and designing seems to be target identification—molecular docking—quantitative structure-activity relationship—lead optimization. Docking is a computational approach that predicts the favored orientation of the binding of one molecule (ligand) to the second molecule (receptor) to form a stable or firm complex. Docking is a software based program used to envisage the affinity and activity of binding of small molecules to their targets by using scoring functions.

Molecular docking software has two core components: (1) a search algorithm (used to find the best conformations of the ligand and receptor); and (2) score function (a measure of how strongly a given ligand will interact with a particular receptor).