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DEVELOPMENT OF COMPUTATIONAL METHOD FOR PSEN MODEL IN PROTEIN-LIGAND DOCKING FOR ALZHEIMER'S DISEASES

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Abstract-Alzheimer's disease is one of the third leading causes of death. It is considered as a neurodegenerative disease which leads the death of brain cells causing memory loss and cognitive decline. According to ratio 5.5 million people around the world are affected by Alzheimer's. The greatest risk factors for Alzheimer's are older age, having a family history of Alzheimer's and carrying the APOE-e4 gene. According to various study themain cause is due to the formation of beta amyloid precursor protein causing senial plaque and tau protein causing neurofibillulary. There are few effective and less expensive treatments and family caregivers are eager to adopt these treatments. Few herald remedies has reported on the benefit of ketone which is an active brain fuel. In this paper we have studied about such few remedies and discussed about the same and how it beneficial in curing the diseases.

Keywords: Alzheimer's disease, Aβ, Senial plaque, active site, Linoleic acid

1. INTRODUCTION

Alzheimer's disease is the most common type of dementia which affects almost 5.5 millions of people worldwide. It is one of the most leading causes of the death among old age, there is no proper cure for Alzheimer. One in every four individuals are diagnosed with Alzheimer's and the number is expected to increase exponentially over the next few years [1]. The history of Alzheimer's dates back to 1901. The first case of Alzheimer's was studied by German psychiatrist Alois Alzheimer.

Alzheimer's is also called as neurodegenerative diseases because it causes significant disruption of neuron's structure and function including the death of neuron. The common symptoms are behavioural change such as inability to recognize pattern, faces, object and problem in communication, impaired judgment and reasoning and change in personality. Loss of memory is one of the most common in Alzheimer's [2]. The main reason for Alzheimer's is aging but it is not normal part of aging. Most people with Alzheimer's are diagnoses above the age 65 they are said to have late onset, people below 65 are said to have early onset of diseases [4]. Aging is not the only reason it is even caused due to mutation. People with familial forms of AD have an autosomal dominant mutation in either one of the presenilin genes located on chromosomes 1 and 14 or in the amyloid precursor protein gene located on chromosome 21. Individuals with Down's syndrome have an increased risk of developing early-onset AD [5].

It is caused by formation of neurofibrillary tangles and senial plaque. Neurofibrillary tangles is caused by tau protein which is belong to family of microtubule associated protein. They are normally caused due to aging. Hyperphosphorylated microtubule-associated tau proteins are the main components of the aggregated filaments found in neurofibrillary tangles which causes Alzheimer's diseases [3].

Theother reason for Alzheimer's is formation of Senial plaque which is caused by amyloid beta protein (Aβ). Amyloid is a general term for protein fragments that the body produces normally. Amyloid plaques are dense, mostly insoluble clumps of protein fragments. Later those small clumps may block cell-to-cell signalling at synapses which later leads to neuronal death [6]. Aβ is cleaved from the large amyloid-precursor protein by secretases, and processing of amyloidogenic pathways produces a 42-amino-acid peptide that can aggregate in the brain under certain conditions [7].

There are few herbal component in nature which shows positive sign in treating Alzheimer's.The study shows that the lack of ketogenic property leads to Alzheimer's.There are various proof that ketones and ketogenic diets could be an effective treatment for degenerative diseases. When we talk about ketone most commonly we talk aboutis coconut oil because of its high ketone property.There are various such component which has high ketones in it.

Coconut oil contains mixture of saturated, monounsaturated and polyunsaturated fats. It is made up of heart healthy polyunsaturated and monounsaturated fats that are important for brain function its growth and development. Linoleic acid is the only fatty acid that makes polyunsaturated fat content of coconut oil. Linoleic acid is important in metabolism. Linoleic acid can be converted into the long chain AAwhich is converted into EPA which is further metabolized to DHA[11]. People

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with Alzheimer's disease have dramatically lower levels of DHA in the neurons of their hippocampus, an area of the brain severely affected by the disease.

2. METHODOLOGY

Alzheimer's disease is caused due to mutation in PSEN, APP, APOE gene. In this study we have modelled a structure for PSEN protein and using docking process docked it to a ligand which act as an inhibitor.

To build a model for PSEN we have used swiss Pdb.Swiss pdb viewer is linked with Swiss model which is an automated homology modelling server developed by SIB. Homology modelling is most reliable method to model a 3D structure of a protein. It uses known or experimentally determined structure to build the related model for given sequence. In this study a known sequence of PSEN protein and a known structure of protein complex whose pdb id 5FNF is used to build the model. Here computational methods was carried out ,for better understanding of binding properties of PSEN protein and Linoleic acid molecule using docking process.For docking process we have used Hex v8.0.0[8] software. After docking the best model was chosen for further studies. Docking is used to predict the preferred orientation of one molecule which is bound to another to form a stable complex. It is mostly used in structure based drug design. Docking process is a computational method to predict position and orientation of a ligand when bound to a receptor here the ligand used is linoleic acid which is a polyunsaturated fatty acid which is important in brain development and memory.The receptor and ligand was clustered by the energy, once docking process was done Pymol software was used for the visualization.PyMOL is an open-source tool to visualize molecules available from (www.pymol.org))[9]. The process of validation of the model was done through choosing the best by analysing the interaction of protein and drug molecule.Tools used in this study are Swiss pdb viewer, PyMol, Hex, Swiss admet property analyser.

3. RESULT

PSEN model is obtained after Homology Modelling using Swisspdb viewer[9]. After modelling the structure the modelled structure had very high force field value which is computed to get the minimum value of -5196.397 and after energy minimization the value is -6609. The model is docked to know the binding site and orientation. The value of the docking process is given in the below Table 1.

Table-1 Value of the docking process

	Cluster	Solution	Models	H-bonds	Bumps	RMS	Etotal	Eshape	Eforce	Eair
model	1	1	0:0	-1	-1	-1.00	-268.30	-268.30	0.00	0.00

ADMET property:SwissADME a free web tool was used to calculate the Pharmacokinetics, drug-likeness, Medical Chemistry ofLinoleic acid molecule[10].The molecules was violatingmuegge(bayer) method and leadlikenessto avoid those violation extra carbon and nitrogen atom was added/removed to get the desired result. The result of ADMET study is given below

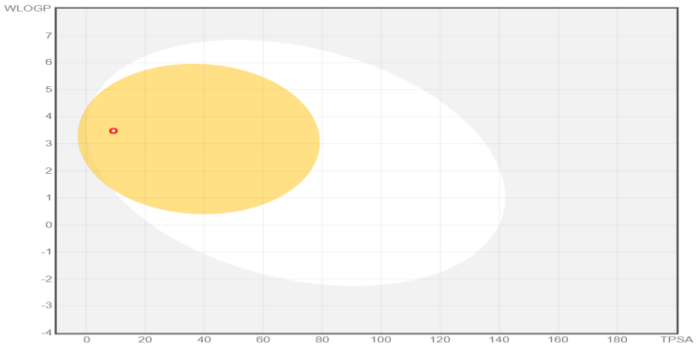

Fig1 According to boiled egg model shown in fig1 the molecule can be passed through blood brain barrier

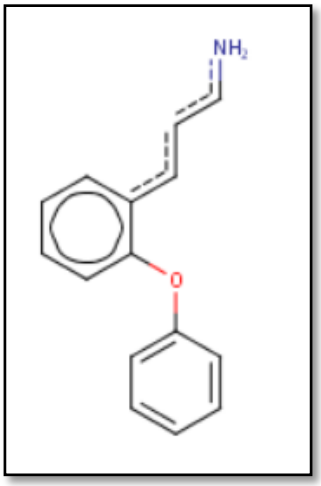

Fig2

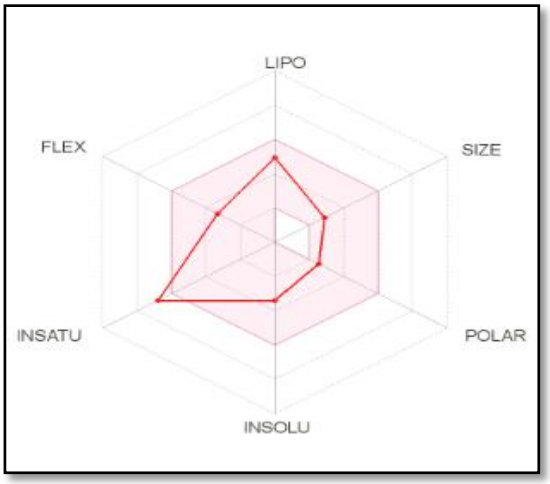

fig3

The pink area in fig3 represents the optimal range for each properties lipophilicity: XLOGP3 between −0.7 and +5.0, size: MW between 150 and 500 g/mol, polarity: TPSA between 20 and 130 $Å^2$, solubility: log S not higher than 6, saturation: fraction of carbons in the sp3hybridization not less than 0.25, and flexibility: no more than 9 rotatable bonds.

Table 1-The physiochemical property table

Formula	C15H17NO
Molecular weight	227.30g/mol
Num. heavy atoms	17
Num. arom. heavy atoms	12
Fraction Csp3	0.20
Num. rotatable bonds	5
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	70.25
TPSA	35.25 Å²

The above table 1 shows the physicochemical properties of the ligand molecule

Table 2-Liphophilicity

Log Po/w (iLOGP)	Log Po/w (XLOGP3)	Log Po/w (WLOGP)	Log Po/w (MLOGP)	Log Po/w (SILICOS-IT)	Consensus Log Po/w
2.83	3.13	3.37	3.20	3.39	3.18

Table 2 shows (Partition coefficient between n-octanol and water, iLOGP, XLOGP3, WLOGP, MLOGP, SILICOS-IT are five different freely available predictive models to calculate Lipophilicity)

Table 3-Water Solubility

Log S (ESOL)	-3.41	Log S (Ali)	-3.54	Log S (SILICOS-IT)	-5.52
Solubility	8.77e-02mg/ml; 3.86e-04 mol/l	Solubility	6.56e-02 mg/ml ; 2.89e-04 mol/l	Solubility	6.91e-04 mg/ml ; 3.04e-06 mol/l
Class	Soluble	Class	Soluble	Class	Moderately soluble

Table 3shows Three different model (ESOL, Ali et al,SILICOS-IT) have been used to predict the water solubility of molecule.

Table 4-Pharmacokinetics

GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (skin permeation)
High	Yes	No	Yes	Yes	Yes	Yes	No	-5.46 cm/s

Table 4 shows the Pharmacokinetics calculation of molecule shows that the GI absorption is high and it permits Blood-Brain Barrier. As the molecule being a substrate to P-Glycoprotein shows poor absorption and bioavailability. Log Kp (skin permeation value) -5.46 shows that skin permeation is moderate which show that administration through skin is possible to delivery the drug. The molecule also acts as a substrate to 4 isoforms of cytochrome P450 (CYP1A2, CYP2C19, CYP2C9, CYP2D6) which is crucial the elimination of drug from the body. The overall result obtain signifies that the oral drug administration is can be of use.

Table 5-Druglikeness

Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score
Yes; 0 violation	Yes	Yes	Yes	Yes	0.55

Table 5 shows the fact that follow all Five Lipinski rule is a favourable chance for the use of the molecule as a drug.

Table 6-Medicinal Chemistry

PAINS	Brenk	Leadlikeness	Synthetic accessibility
0 alert	0 alert	No; 1 violation: MW<250	1.92

Table 6 shows PAINS, Brenk are two pattern recognition methods allow for identification of potentially problematic fragments.

4. CONCLUSION

As above mentioned molecule can be used as a drug which has bound to the protein PSEN. So we are suggesting that PSEN may be the target based on the overlap of receptor-based pharmacophores and docking into the crystal structure. FDA has already approved drugs that could target this protein-ligand interaction.in docking process. Computational methods can be easily compared with the wet lab experimental methods. We can use thesecomputational method for the other disease which does not have a proper treatment.

5. REFERENCE

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