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IN-SIlico Docking Analysis of Sterculia Lychnophora Compounds against Proteins Causing Alzheimer's Disease

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ABSTRACT: Alzheimer's disease is the most common cause of dementia. Amyloid Precursor Protein (APP) responsible for Alzheimer's disease to inhibit the function of this protein the cerebrosides compounds soyacerebroside I(ligand 1) and 1-O-beta-D-glucopyranosyl-(2S,3R,4E,8Z)-2-[(2-hydroxyoctadecanoyl)amido]-4,8-octadecadiene-1,3-diol (ligand 2) a used as ligand. The highest binding energy is obtained using docking analysis and the protein-ligand interaction is studied where possible binding sites are predicted. Thus these compounds can be used drug against Alzheimer's disease and for further analysis.

***Keywords*- Sterculia lychnophora, Alzhiemer's disease, Cerebrosides, In Silico**

I. INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder and the most common cause of dementia. The number of people living with dementia will almost double every 20 years[1]. AD is encompassing the deterioration of cognitive functions and behavioral changes, characterized by the aggregation of amyloid β-protein (Aβ) into fibrillar amyloid plaques in selected areas of the brain. High levels of fibrillary Aβ, the main constituent of senile plaques, are deposited in the AD brain that results in the loss of synapses, neurons and impairment of neuronal function [2].In the past decade, genes causing familial forms of such disorders have been identified, protein pathways involving the gene products have been delineated, and specific treatments directed at these pathways have begun to enter human trials[3]. Cerebrosides is the common name for a group of glycosphingolipids which have a single sugar linked to ceramide those with galactose are characteristically found in the plasma membranes of cells in neural tissue[4]. This kind of compounds has already been highly expected in the treatment of mental dysfunctions such as Alzheimer's disease. The presence of cerebrosides in the seeds of *S. lychnophora* was reported to be neuro protective effect of one of these cerebrosides by bioactivity screening [5].

In pharmacology hypothesis development and testing the *In silico* (computational) methods have been developed and widely applied. These *in silico* methods include database searching, quantitative structure-activity relationships, similarity searching, pharmacophore identification, computational modeling and docking; these methods have seen use in the discovery and optimization of novel molecules with affinity to a target [6]. As the two cerebrosides compounds Soyacerebroside-I and 1-*O*-beta-D-glucopyranosyl-(2*S*,3*R*,4*E*,8*Z*)-2-[(2-hydroxyoctadecanoyl)amido]-4,8-octadecadiene-1,3-diol was found in *Sterculia lychnophora* [5]. The aim of study is to use these compounds as inhibitors against amyloid beta precussor proteins of Alzhiemer's disease using docking approach and the highest binding energy in negative indicates the more likely to be used this compounds as drugs in future.

II. METHODS AND MATERIALS

A. Selection of Ligands

Two cerebrosides (soya-cerebroside I and 1-O-beta-D-glucopyranosyl-2S,3R,4E,8Z)-2-[(2-ydroxyoctadecanoyl) amido]-4,8-octadecadiene-1,3-diol) were selected which found to be present in *Sterculia lychnophora* which may act as ligand against Alzheimer's disease proteins.

These ligands was retrieved from NCBI Pub Chem Compound database, The 2D and 3D structure of the ligand was shown in figure 1 and 2 respectively. The structure was downloaded in SDF format and was then converted to PDB format and further used for docking studies.

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B. Selection of target

The Kyoto Encyclopedia of Genes and Genome pathway database (KEGG) was the source of metabolic pathway information. It was found that different proteins were responsible for cause of Alzheimer's disease.
Our study was on amyloid precursor protein (APP), four structures of APP (1AAP, 3KTM, 3IFN and 3UHM) were downloaded from PDB in PDB file format and complete sequence of APP was obtained from UniProtKB by downloading the fast format. Swiss Model was used for modeling the sequence retrieved from UniProtKB. The energy minimization of modeled protein was performed by SPDV and its score was obtained. Then the active sites of these proteins were obtained from online active site prediction tool. The Ramachandran plot was obtained to study the favorable regions with residues present.

Fig 1: 3D Structure of Soyacerebroside- I (ligand 1).

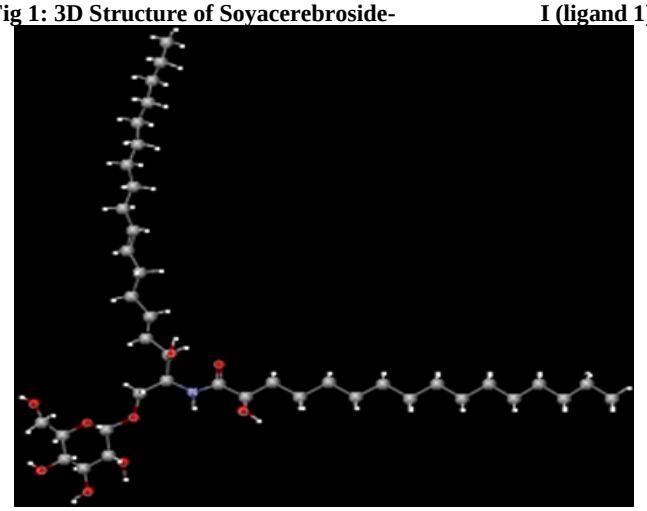

Fig 2 : 3D Structure of 1-*O*-beta-D-glucopyranosyl-(2*S*,3*R*,4*E*,8*Z*)-2-[(2-hydroxyoctadecanoyl)amido]-4,8-octadecadiene-1,3-diol (ligand 2)

C. Protein optimization

Prior to docking hydrogen bonds were added and water molecules and hetero atoms were removed from all five proteins by using Discovery Studio version-3.5 Accelrys Software.

D. Docking

The docking of selected five proteins with two ligands was performed by using Hex 6.3 software. The receptor and the ligand molecule were loaded from open option then the docking was started by selecting docking option

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from control. The Hex message box showed the Etotal scores which showed the best score for a particular protein with ligand.

III. RESULTS AND DISCUSSION

Docking is done by hex 6.3 tool for 4 protein obtained from PDBid and one modeled protein by Swiss model against two ligand soyacerebroside I(ligand 1) and1-*O*-beta-D-glucopyranosyl-(2*S*,3*R*,4*E*,8*Z*)-2-[(2-hydroxyoctadecanoyl) amido]-4,8-octadecadiene-1,3-diol (ligand 2).

The selection of proteins was done by finding the secondary structure and favorable regions of protein by Ramachandran plot. The selected five proteins were docked with the two ligands in Hex 6.3 software; the Etotal score with the protein ligand interaction in 2D view was obtained. Out of the five proteins the energy minimization of APP modeled structure from Swiss model was done using SPDBV software.

The docking study showed that ligand 1 (soyacerebroside I) and ligand 2 (1-O-beta-D-glucopyranosyl-(2S,3R,4E,8Z)-2-[(2-hydroxyoctadecanoyl)amido]-4,8-octadecadiene-1,-3-diol) was having Etotal but better result score against 3IFN protein was shown by the ligand 1 since it was having highest negative score compared to ligand 2.

The protein-ligand interaction plays a significant role in drug designing. The two receptors are 3IFN gets bind to ligand form receptor ligand complex. The interaction of 3IFN with ligand 1(soyacerebroside -I) helps in analyzing the binding properties of the protein to its inhibitors. The ligand 1 had binding energy -389 with 3IFN protein receptor whose score was highest and ligand 2 had binding energy 375.9 with 3IFN protein receptor.

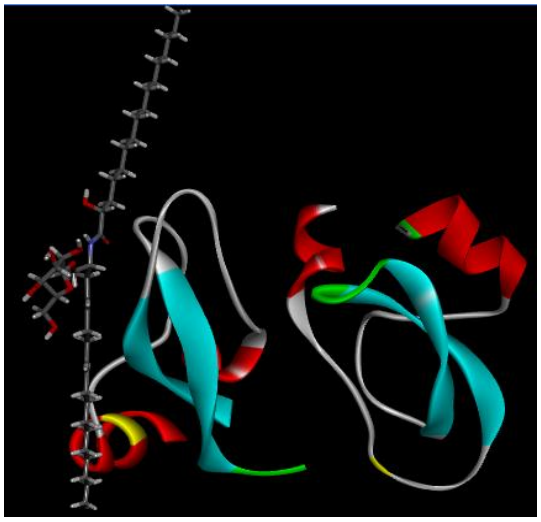

Fig 3: Docking diagram of 1AAP Protein

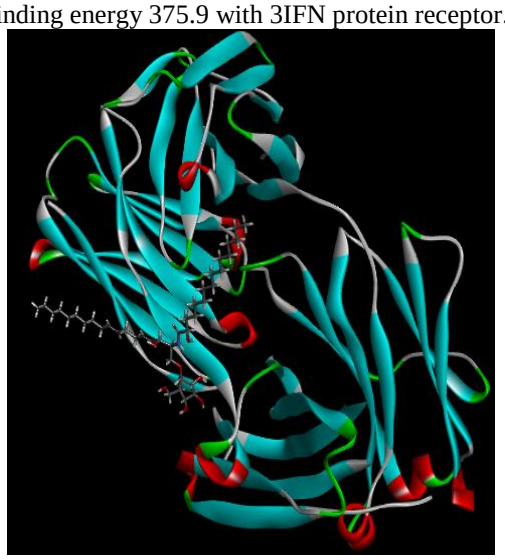

Fig 4 : Docking diagram of 3IFN Protein Receptor Receptor ligand 1 and ligand 1

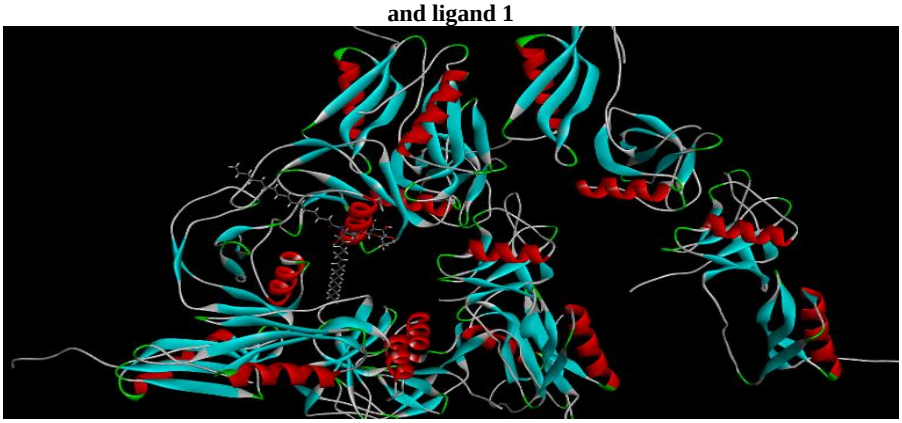

Fig 5 : Docking diagram of 3KTM Protein Receptor and ligand 1

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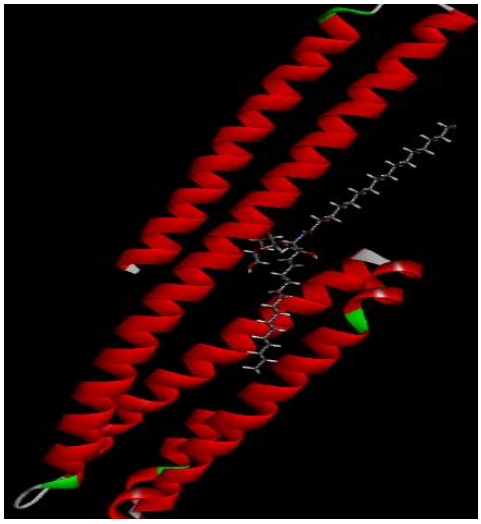

Fig 6 : Docking diagram of 3UMH Protein and ligand 1

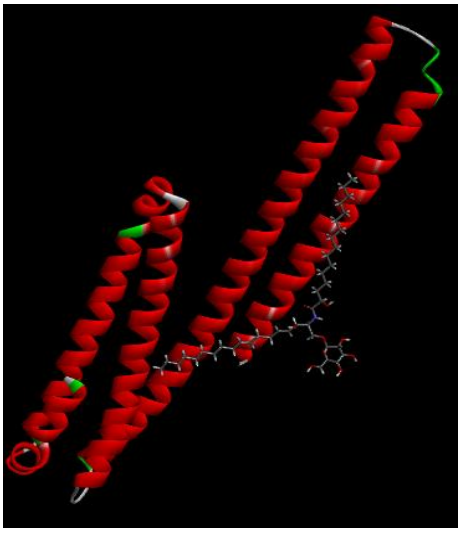

Fig 7 : Docking diagram of modelled receptor and ligand 1

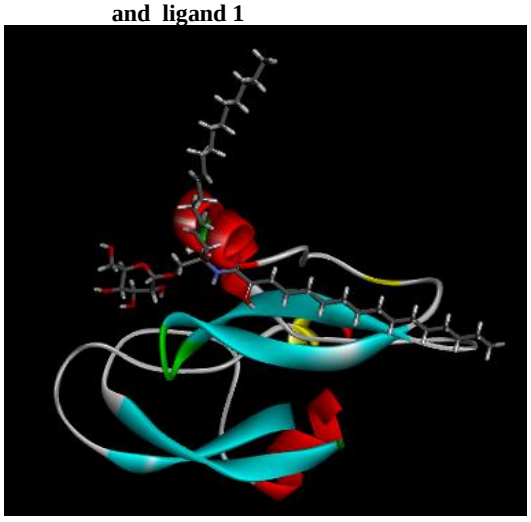

Fig 8 :Docking diagram of 1AAP Protein Receptor and ligand2 molecule

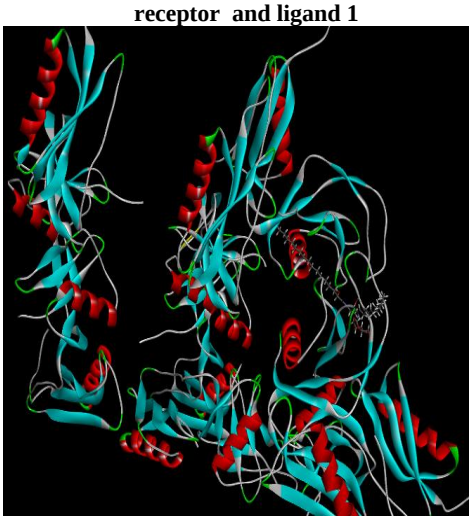

Fig 9:Docking diagram of 3KTM Protein and ligand 2 molecule

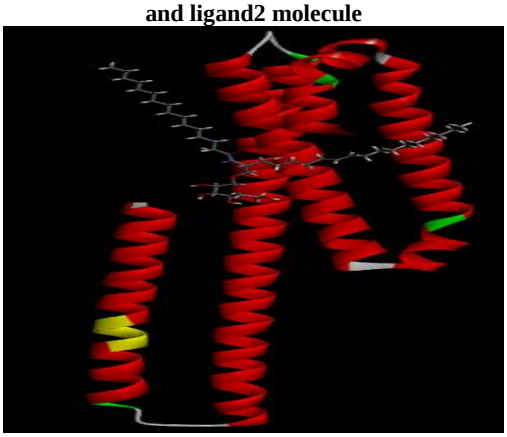

Fig 10: Docking diagram of 3UMH Protein Receptor and ligand2 molecule

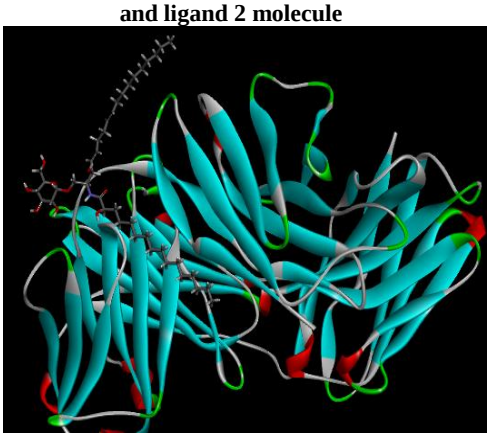

Fig 11: Docking diagram of 3IFN Protein and ligand 2 molecule

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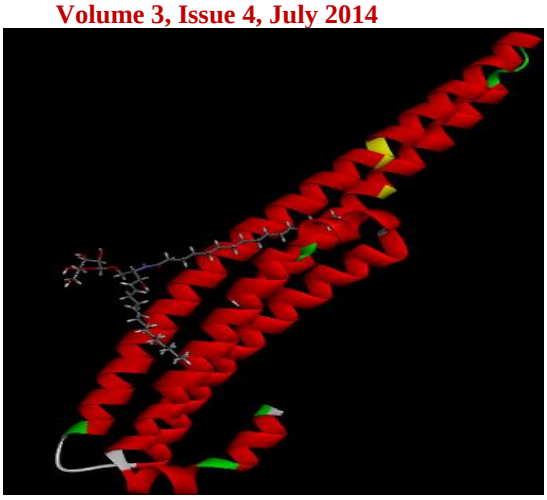

Fig 12: Docking diagram of ligand 2 and Target protein modeled by swiss model.

Inhibitors	Target	Binding Energy
Ligand 1	1APP	-327.3
	3KTM	-239.1
	3UMH	-375.8
	3IFN	**-389.0**
	model	-377.8

Table 1: E-score for the docked result of soyacerebroside I against 5 target protein.

Inhibitors	Target	Binding Energy
Ligand 2	1APP	-298.1
	3KTM	-289.6
	3UMH	-359.6
	3IFN	**-375.9**
	model	-363.1

Table 2: E-score for the docked result of 1-*O*-beta-D-glucopyranosyl-(2*S*,3*R*,4*E*,8*Z*)-2-[(2-hydroxyoctadecanoyl)amido]-4,8-octadecadiene-1,3-diol against 5 target protein.

Keys-

- ✓ Ligand 1: Soyacerebroside I
- ✓ Ligand 2: 1-*O*-beta-D-glucopyranosyl-(2*S*,3*R*,4*E*,8*Z*)-2-[(2- hydroxyoctadecanoyl)amido]-4,8-octadecadiene-1,3-diol
- ✓ 1AAP, 3KTM, 3UMH, 3IFN are PDBid.
- ✓ Model is the protein which is
- ✓ Modeled by Swiss model server.
- ✓

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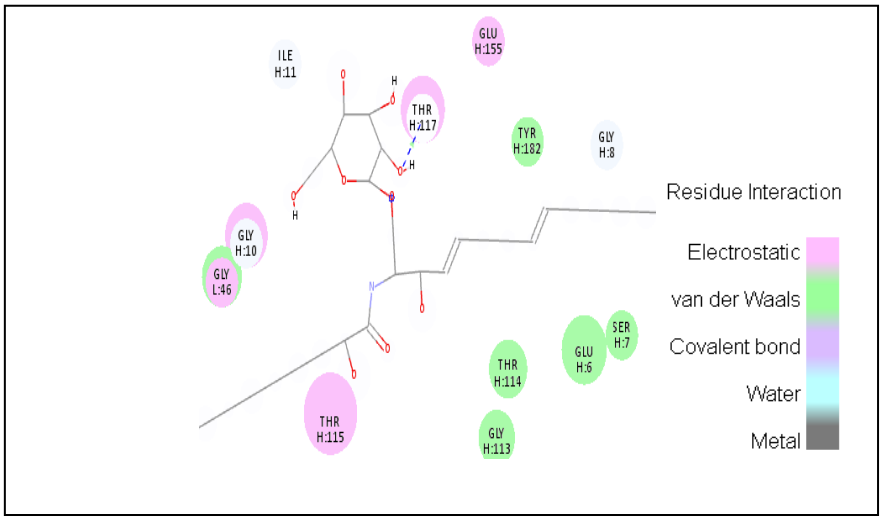

Fig 13: Interaction diagram of 3IFN Protein Receptor and ligand 1

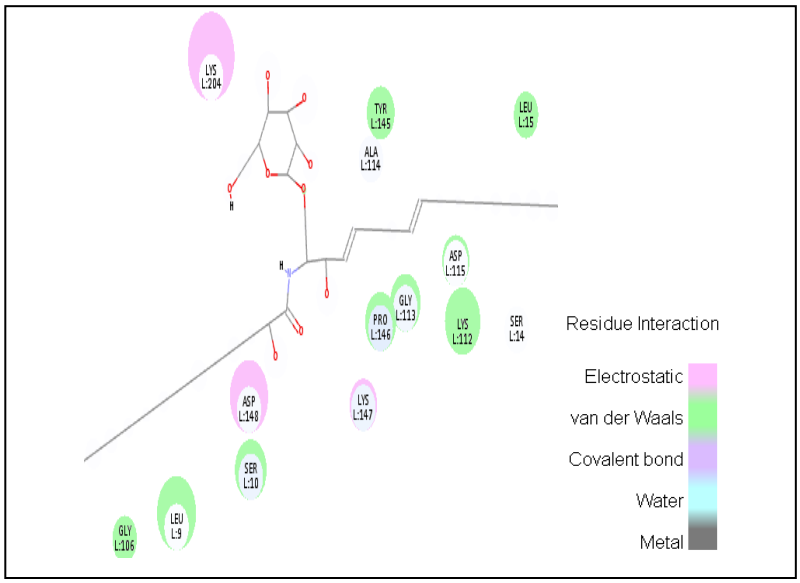

Fig 14: Interaction diagram of 3IFN receptor and ligand 2

Target	Ligands		
		Electrostatic interaction residue	Vander Waals interaction residue
3IFN	1	GIU:H:155, THR:H:117,GLY: H:10, GLY H:46,THR:H:115.	TYR:H:182,THR:H:114,GLY: H:113,GLU:H:6,SER:H:7
3IFN	2	LYS:L:204, ASP: L:148, LYS:L:147	TYR:L:145, LEU:L:15, LYS:L: 112, GYL:113, PRO:L:146 ASP:L:115, SER:L:10, LEU:L:9

Table 3: Possible Binding Site Residue with 3IFN Protein Target to ligand 1 and 2

IV. CONCLUSIONS

Alzheimer's disease is the most prevalent dementia related disease. Cerebrosides compounds showed neuroprotective effect which is present in *Sterculia lychnophora* [5]. The docking study showed that ligand 1 (soyacerebroside I) and ligand 2 (1-O-beta-D-glucopyranosyl-(2S,3R,4E,8Z)-2-[(2-

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hydroxyoctadecanoyl)amido]-4,8-octadecadiene-1,3-diol) was having high Etotal score against 3IFN protein but better result was shown by the ligand 1 since it was having highest negative score compared to ligand 2.

The protein-ligand interaction plays a significant role in drug designing. The two receptors are 3IFN gets bind to ligand from receptor ligand complex. The protein-ligand has electrostatic and Vander Waals interaction residues. These sites could be the best possible binding sites to inhibit the 3IFN protein. In order to prevent the activity of these proteins there is an urgent need to identify inhibitors with minimal side effects. So an attempt has been made to identify the cerebrosides derivatives as probable Anti-Alzheimer's drugs by Molecular Docking studies.

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