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PROVING THE EFFICACY OF MANGIFERIN AS A NEUROPROTECTIVE DRUG USING DOCKING STUDIES

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Abstract: Mangiferin, a bioactive Xanthonoid known for its anti-oxidant & therapeutic activity, has been involved in a variety of potential pharmacological activities. The aim of this work is to prove the efficacy of mangiferin as a neuroprotective drug by docking it with β-amyloid precursor protein, which causes Alzheimer's. Alzheimer's disease (AD) is a progressive neurodegenerative disease, which is characterized by progressive cognitive deterioration and behavioral changes along with the chronic inflammation of neurons. Studies have shown that the deposition of amyloid-β (Aβ) peptide has resulted in the inflammatory changes such as astrocytosis and microgliosis. Based on the quantitative analysis of the molecular docking technique it was observed that mangiferin successfully docked with amyloid-β (Aβ) peptide. The ligand binding affinity was high due to the presence of many flexible docked conformers. The most stable conformer was having a final docked value of -12.421 with binding energy amounting to -4.11 kcal/mol. The *in silico* docking analysis demonstrates that mangiferin exhibits binding interactions with β-amyloid precursor protein that are potentially responsible for the inhibition of the protease enzyme which would be helpful in developing a neuroprotective drug for Alzheimer's Disease.

Keywords: Mangiferin, β-amyloid peptide (Aβ), Alzheimer's disease, AutoDock, Binding Energy

Introduction

Mangiferin (1,3,6,7-tetrahydroxyxanthone-C-2-*β*-D-glucoside, MGF), a constituent of *Curcuma amada* (Padmapriya *et al*. 2012) has been reported to have multiple pharmacological potentials like antioxidant activity, immunomodulatory effect, anti-inflammatory effect, effect of improvising dyslipidemia, therapeutic effect on periodontal disease and antidiabetic effect on both type 1 as well as type 2 diabetes (Guha *et al*.1996, Dar *et al.* 2005, Bhowmik *et al*. 2009, Niu *et al.* 2012, Duang *et al*. 2011). The importance of mangiferin lies with its radical scavenging activity (Miliauskas *et al*. 2004), inhibition of oxidative stress (Murunganandan *et al.* 2005) and its ability to form a complex with Iron (III) (Ghosal *et al*. 1996).

Alzheimer's disease (AD) is a progressive neurodegenerative disease, which is characterized by progressive cognitive deterioration and behavioural changes along with the chronic inflammation of neurons. AD is one form of dementia that gradually increases with time. Dementia is a loss of brain function that occurs with aging & certain diseases. AD is characterized by accumulation of the amyloid-β (Aβ) peptide and microtubule associated protein tan within the brain. Most often, AD is diagnosed in people over 65 years of age (Brookmeyer *et al* 1998). There are two types of onset- late and early. Genetic, biochemical and behavioural research suggest that physiological generation of a neurotoxic Aβ peptide from sequential amyloid precursor protein (APP) by proteolysis is the crucial step in the development of AD.

APP is a single-pass trans-membrane protein expressed at high levels in the brain and metabolized in a rapid and highly complex fashion by a series of sequential proteases, including the intramembranous ϒ-secretase complex, which also processes other key regulatory molecules. Alzheimer's amyloid beta-protein precursor contains a Kunitz protease inhibitor domain (APPI) potentially involved in proteolytic events leading to cerebral amyloid deposition. Genetic studies of APP processing will be crucial to the development of therapeutic targets to treat Alzheimer's (O'Brien RJ & Wong PC, 2011).

Protein-ligand docking was performed between the molecular models of amyloid precursor protein (1AAP) and mangiferin (MGF).

Methods

Softwares: AutoDockTools (ADT) and AutoDock 4.2 was downloaded from www.scrippps.edu. PyMol was downloaded from https://pymol.org.

Protein preparation for docking: The 3D structure of Amyloid beta precursor protein (PDB ID-1AAP) was downloaded from RCSB Protein Data Bank (PDB) (https://www.rcsb.org/pdb/explore.do?structureId=1AAP), before initiating the docking simulations (Hynes *et al*. 1990). The original bimolecular structure was reduced to a unimolecular receptor by using PyMol. 1AAP was modified by adding polar hydrogens and then kept rigid in the docking process whereas all the torsional bonds of ligands were set free by Ligand module in AutoDockTools. Gasteiger charges were computed followed by creation of grid maps using AutoGrid 4.2.

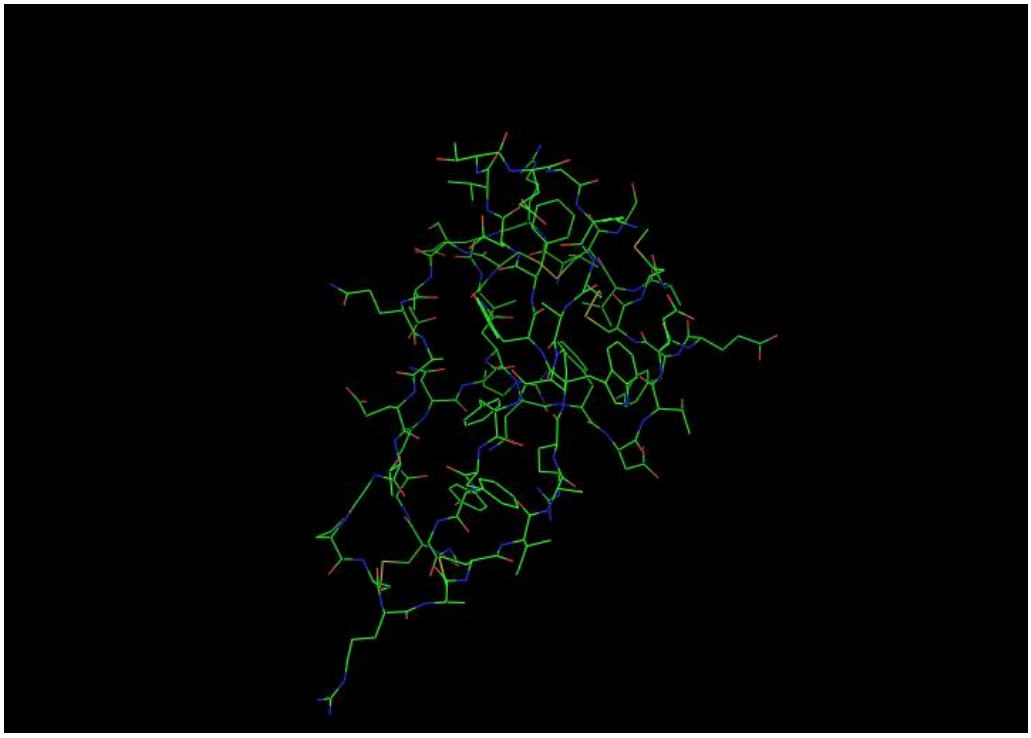


Figure 1: The three dimensional structure of amyloid-β precursor protein (PDB: 1AAP)

Ligand preparation for docking: The 3D structure of the ligand Mangiferin (CID-5281647) was downloaded from PubChem Open Chemistry Database (https://pubchem.ncbi.nlm.nih.gov/compound/Mangiferin) and was optimized using AutoDockTools.

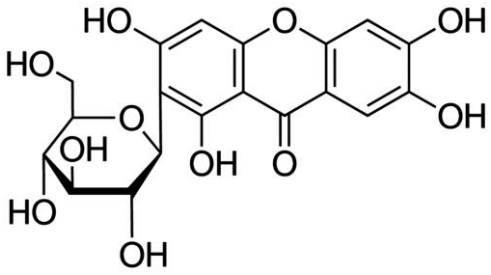


Figure 2: Parental Structure of Mangiferin

Molecular Docking: Molecular docking simulations were carried out using AutoDock 4.2 in AutoDockTools. The autodock 4.2 program was used to investigate the ligand binding with the amyloid beta precursor protein using a grid spacing of 0.5 Å and the grid points in X, Y and Z axis were set to 100 x 100 x 100 Å. The search was based on the Lamarkian Genetic Algorithm (Oprea et al., 2001) and the results were analysed using the binding energies. Top 10 conformers were ranked in order of increasing docking energies.

Results:

The docked positions of mangiferin into the binding site was explored using AutoDockTools software which is considered to be one of the most powerful tool for molecular recognition. The ligand mangiferin was used for the *in silico* docking analysis on amyloid-β precursor protein receptor (PDB: 1AAP). Molecular docking methods are commonly used for predicting binding modes to proteins and energies of ligands (Bikadi and Hazai, 2009). Docking was accomplished using AutoDock 4.2 which is a set of automated docking tools which was used to predict the binding affinity, activity and orientation of mangiferin to our docked target protein molecule. The analysis was based on the final score of docked conformations, free energy of binding values and Inhibition constant (Ki) of the conformers detected. Free energy of binding is calculated as a sum of four energy components (1) Final Intermolecular Energy *(Van der walls forces', hydrogen bonds, desolvation energy & electrostatic energy),* (2) Total Internal Energy, (3) Torsional free energy and (4) Unbound system energy. Mangiferin was found to bind at various active sites of amyloid-β precursor protein with lowest estimated free binding energy found to be -4.11 kcal/mol along with the estimated inhibition constant (K**i**) corresponding to 974.11μM (micromolar) at 298.15K temperature. The respective values for each conformer are listed in **Table 1** whereas the docked conformers are shown in **Figure 3 and 4**. The *in silico* experiment demonstrates that mangiferin binds with β-amyloid precursor protein thereby inhibiting the Kunitz protease domain which is potentially involved in the proteolytic events leading to cerebral amyloid deposition. Thus we can hypothesize that mangiferin may play an important role in inhibiting the protease activity present in the amyloid-β protein. Mangiferin can therefore be a promising candidate for the development and design of a neuroprotective drug with therapeutic activities.

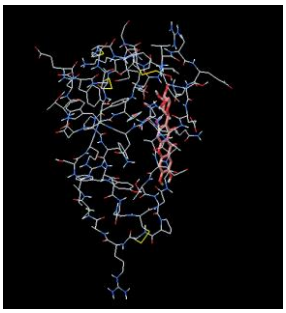
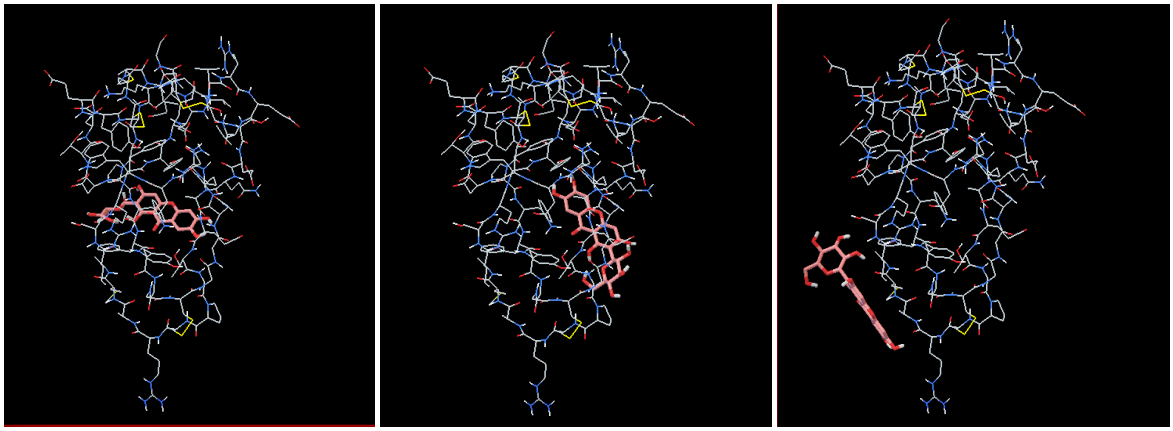
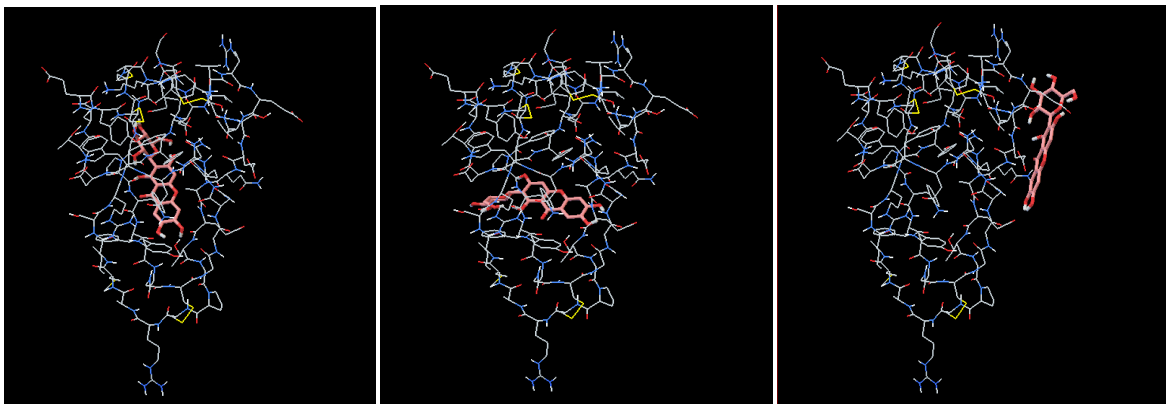


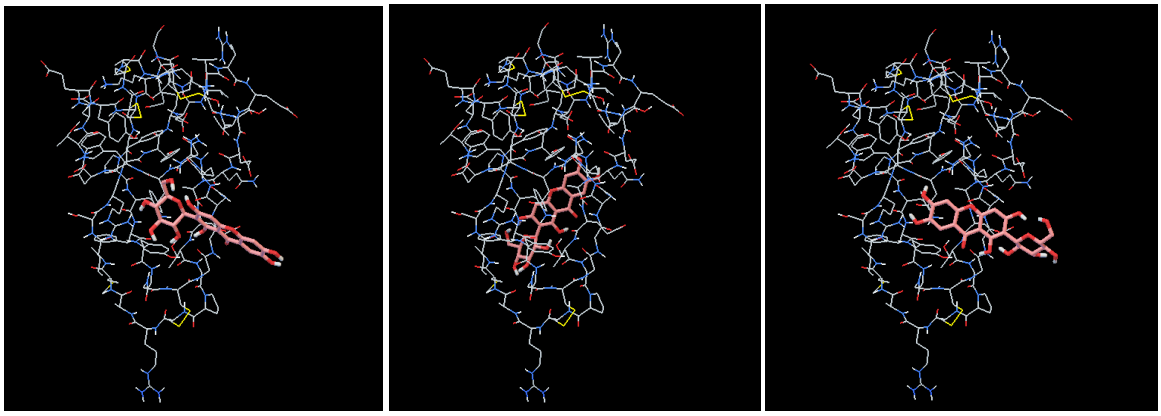
Figure 3: Most stable docked conformer (A) showing the interaction of mangiferin with β-amyloid precursor protein receptor.



(B) *(C)* *(D)*



(E) *(F)* *(G)*



(H) *(I)* *(J)*

Figure 4: Docked conformers ranked in order of stability

Table 1: Docking results of Mangiferin docked onto amyloid-β precursor protein receptor

Sl. No.	Run	*Conformer*	*Final Docked Value*	*Estimated Free Energy Binding (in kcal/mol)*	*Estimated Inhibition Constant, Ki (at 298.15K)*
1	6	A (most stable)	-12.421	-4.11	974.11μM
2	5	E	-12.513	-3.84	3.84mM
3	10	J	-11.223	-3.35	3.48mM
4	8	H	-9.661	-3.22	4.39mM
5	7	G	-11.637	-3.12	5.14mM
6	2	B	-12.109	-3.11	5.25mM
7	3	C	-11.739	-2.81	8.73mM
8	9	I	-10.978	-2.40	17.27mM
9	4	D	-10.797	-2.33	19.45mM
10	1	F	-10.727	-2.19	24.78mM

Number of distinct conformational clusters found: 9 out of 10 runs, using RMSD tolerance 2Å

Conclusion

In conclusion, the results of the present study demonstrates that the *in silico* molecular docking studies of mangiferin with amyloid-β precursor protein receptor exhibits binding interactions that are potentially responsible for the inhibition of the protease enzyme and further studies are needed for the development of a potential neuroprotective drug for the treatement of Alzheimer's disease.

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