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Research Article

Molecular docking of fisetin as a multi-target drug in the treatment of Parkinson's disease

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ABSTRACT

Fisetin is found in various fruits and vegetables. It is reported to have neurotropic, anti-inflammatory, anti-carcinogenic and also other health benefits. Fisetin has been proved to have neuroprotective effect against Parkinson's disease (PD). Elucidation of the molecular interaction of fisetin with various anti-parkinsonian drug targets leads to better understanding mode of action of the drug. The present study is aimed to study the molecular interaction of fisetin with molecular targets having potential role in PD. The molecular properties and drug likeness model score were first analysed for flavonoid fisetin, which was found to be 0.76. The structures of the molecular drug targets, such as MAO A (2BXR), MAO B (2BYB), COMT (2AVD) and tyrosine hydroxylase (2XSN), was extracted from RCSB-Protein Data Bank. Molecular docking was performed using AUTO DOCK-4.2. The docking scores were evaluated by analyzing the minimum binding energy for the first five runs for all the target proteins. The minimum binding energy for MAO A (2BXR), MAO B (2BYB), COMT (2AVD), tyrosine hydroxylase (2XSN) were -10.22 kcal/mol, -9.68 kcal/mol, -7.45 kcal/mol and -6.67 kcal/mol respectively. Out of the 4 potential PD drug targets, MAO A and MAO, genes responsible for oxidative deamination of dopamine, are predicted to have the least minimum binding energy and best interaction with fisetin.

Keywords: Fisetin, docking, multidrug targets, autodock, MAO A, MAO B, COMT, Tyrosine hydroxylase

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INTRODUCTION

Parkinson's disease is characterized by progressive loss of dopaminergic neurons in the substantia nigra, leading to the loss of motor skills¹⁻⁴. The key causative factors that might influence disease outcomes include buildup of reactive oxygen species (ROS), selective loss of neurons, loss of mitochondrial membrane potential and ATP depletion⁵. Flavonoid, fisetin has gained great interest due to its diverse pharmacological effects, such as antioxidant, anti-inflammatory, anticancer and antihypertensive action, among others⁶. The impaired function of Parkinson disease can be ameliorated by using flavonoid fisetin, which has high antioxidative and neuroprotective activities⁷.

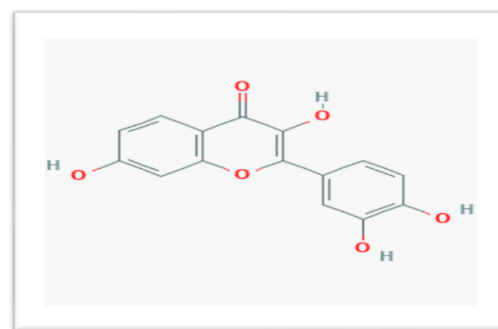


Figure 1: Molecular structure of fisetin.

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The emerging neuroprotective therapies are not effective due to restricted understanding of the important molecular event that stimulate neurodegeneration. The causes PD pathogenesis is thought to be due to the misfolding of proteins, dysfunction mitochondria & the ubiquitin proteasome pathway, oxidative stress and deregulation dopamine metabolism⁸. The major enzymes involved in dopamine metabolism include MAO A, MAO B, COMT - involved in dopamine degradation and tyrosine hydroxylase - involved in dopamine synthesis. The main objective of this study was to dock the flavonoid fisetin as ligand with the molecular targets of Parkinson's disease. In silico methods are regularly used in modern drug design to help apprehend drug-target protein interactions. The results obtained from this study would be useful in understanding the mechanism of neuro-protective effect of fisetin.

MATERIALS AND METHODS

Preparation of the protein and Ligand Structures

The three dimensional X-ray structure of MAO A (2BXR), MAO B (2BYB), COMT (2AVD), tyrosine hydroxylase (2XSN) was obtained from RCSB Protein Data Bank. The structure was refined by removing water molecules and other complexed molecules. Hydrogen atoms were added and electronic charges were assigned to the protein atoms using Kollman united atoms force field by using AutoDockTools-1.5.6⁹. The gasteiger partial atomic charges were added and all possible flexible torsion angles of the ligand was defined by using AUTOTORS. The structures were saved in a PDBQT format for AutoDock calculations.

The ligand fisetin structure was drawn using chemsketch. To understand the molecular interaction of fisetin, blind docking of fisetin onto MAO A (2BXR), MAO B (2BYB), COMT (2AVD) and tyrosine hydroxylase (2XSN) proteins was carried out. The docking calculations were carried out using

both the Genetic Algorithm and Lamarckian Genetic Algorithm.

Docking Studies and Drug likeness

Docking calculations were performed to predict the binding affinity between the fisetin and MAO A (2BXR), MAO B (2BYB), COMT (2AVD), tyrosine hydroxylase (2XSN) proteins using AutoDock 4.2¹⁰. AutoDock requires precalculated grid maps, one for each atom type present in the ligand being docked. These maps were calculated by using the auxiliary program AutoGrid. The compounds treated as flexible molecules were allowed to move in the six spatial degrees of freedom for orientation and torsional degrees of freedom within the grid box.

AutoDock uses a semi empirical free energy force field to evaluate conformations during docking simulations. The energy functions define what contributes to the energy of the molecule, like bond stretching, bending etc., so that energy of the molecule can be calculated for any particular conformation. The force field evaluates binding in two steps. In the first step, the intramolecular energetics is estimated for the transition from unbound states to the conformation of the ligand and protein in the bound state. The second step then evaluates the intermolecular energetics of combining the ligand and protein in their bound conformation.

$$\Delta G = \Delta G_{vdw} + \Delta G_{bond} + \Delta G_{elec} + \Delta G_{tor} + \Delta G_{desolv}$$

First three terms are for van der Waal's, hydrogen bonding, electrostatics respectively. The term ΔG_{tor} is for rotation and translation and ΔG_{desolv} is for desolvation upon binding and the hydrophobic effect¹⁰. Drug-Likeness and molecular property prediction for the fisetin was done by molsoft.

RESULTS AND DISCUSSION

The first best five minimum binding energy of fisetin with the 4 drug targets are shown in following table.

Table 1: Minimum Binding Energy of fisetin with the 4 drug targets of the top hits

2BXR: MAO A			2AVD: COMT		
S. No	Run	Minimum Binding Energy	S. No	Run	Minimum Binding Energy
1	8	-10.22 kcal/mol	1	6	-7.45 kcal/mol
2	5	-10.07 kcal/mol	2	7	-7.36 kcal/mol
3	10	-9.63 kcal/mol	3	8	-7.26 kcal/mol
4	1	-9.51 kcal/mol	4	9	-7.22 kcal/mol
5	4	-8.98 kcal/mol	5	5	-6.9 kcal/mol
2BYB: MAO B			2XSN: tyrosine hydroxylase		
S. No	Run	Minimum Binding Energy	S. No	Run	Minimum Binding Energy
1	6	-9.68 kcal/mol	1	7	-6.67 kcal/mol
2	7	-9.42 kcal/mol	2	6	-6.48 kcal/mol
3	1	-9.02 kcal/mol	3	9	-6.6 kcal/mol
4	5	-8.69 kcal/mol	4	4	-6.31 kcal/mol
5	8	-8.81 kcal/mol	5	10	-6.56 kcal/mol

Table 2: Lowest binding energy of fisetin with the 4 drug targets of the top hits

S.No.	Protein	Final Intermolecular Energy (vdW + Hbond + desolv Energy+Electrostatic Energy)	Final Total Internal Energy	Torsional Free Energy	Unbound System's Energy
1	MAO A	-11.71 kcal/mol	-1.34 kcal/mol	+1.49 kcal/mol	-1.34 kcal/mol
2	MAO B	-11.18 kcal/mol	-1.37 kcal/mol	+1.49 kcal/mol	-1.37 kcal/mol
3	COMT	-8.94 kcal/mol	-0.94 kcal/mol	+1.49 kcal/mol	-0.94 kcal/mol
4	tyrosine hydroxylase	-8.17 kcal/mol	-1.63 kcal/mol	+1.49 kcal/mol	-1.63 kcal/mol

Figure 2 shows the lowest binding energy conformation of fisetin with MAO, Figure 3 shows the lowest binding energy conformation of fisetin with MAO B. Figure 4 shows the lowest binding energy conformation of fisetin with COMT. Figure 5 shows the lowest binding energy conformation of fisetin with tyrosine hydroxylase. These structures are visualized using chimera ¹¹. The red color denotes oxygen atom in the ligand fisetin and the blue and orange colored lines denotes the interaction between ligand and the protein molecules.

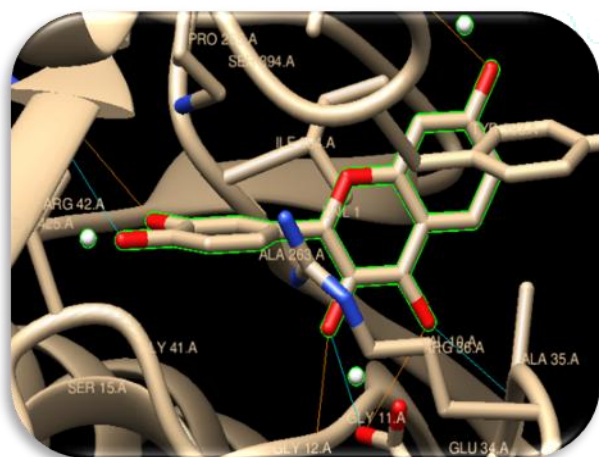


Figure 2: (2BXR-A: MAOA)

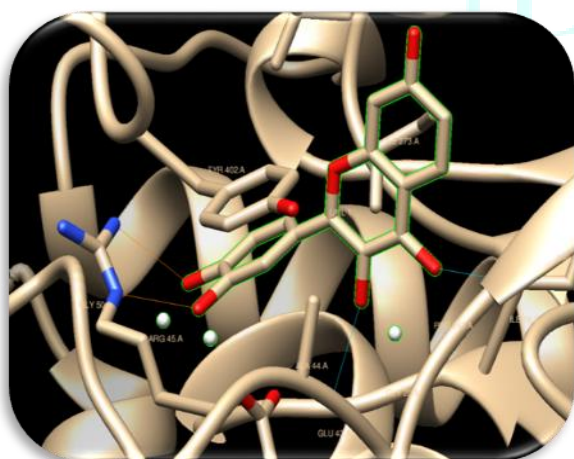


Figure 3: (2BYB-A: MAOB)

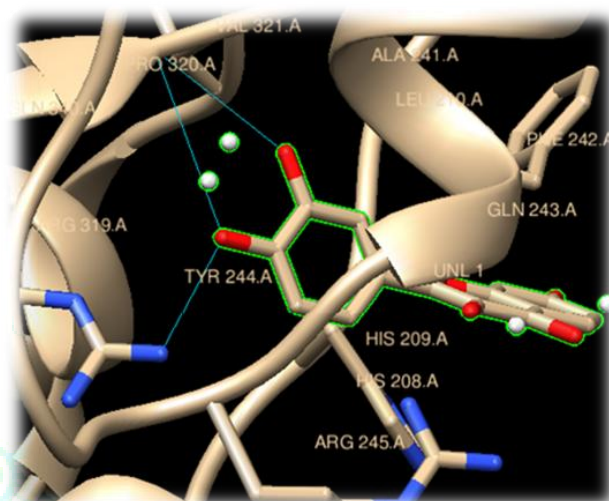


Figure 4: (2AVD-A: COMT)

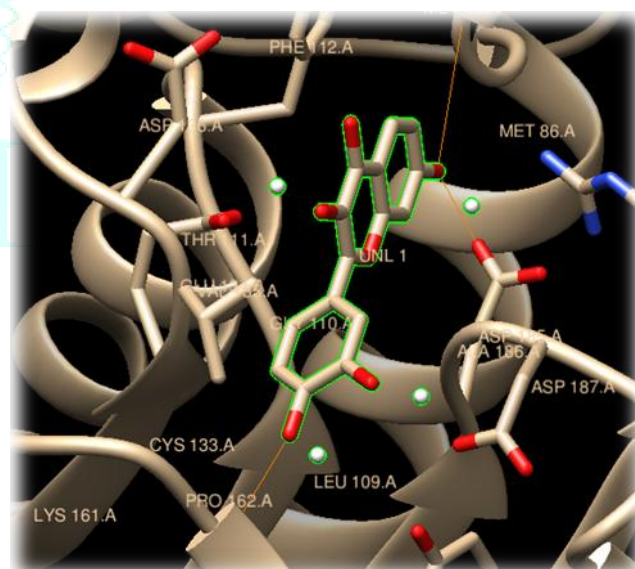


Figure 5: (2XSN-A: tyrosine hydroxylase)

Drug likeness model score of fisetin was 0.76, shown in figure 6. The molecular properties of fisetin is shown below

Molecular Properties of fisetin using molsoft

Molecular formula: C₁₅ H₁₀ O₆
Molecular weight: 286.05
Number of HBA: 6
Number of HBD: 4
MolLogP : 2.49
MolLogS : -3.93 (in Log(moles/L)) 33.33 (in mg/L)
MolPSA : 86.06 Å²
MolVol : 271.53 Å³
Number of stereo centers: 0

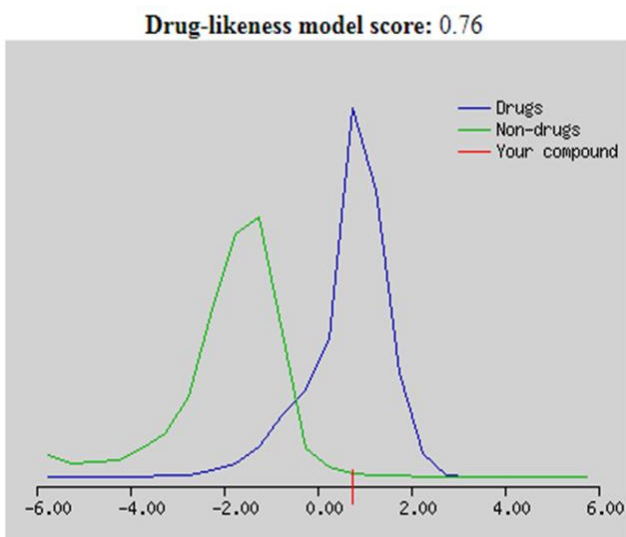


Figure 6: Drug likeness model score of fisetin

CONCLUSION

In the present study, the binding and interactions of fisetin with MAO A (PDB ID: 2BXR), MAO B (PDB ID: 2BYB), COMT (PDB ID: 2AVD), tyrosine hydroxylase (PDB ID: 2XSN) proteins have been studied using molecular docking calculations. Fisetin has shown significant binding interactions with the MAO A (PDB ID: 2BXR), MAO B (PDB ID:

2BYB), COMT (PDB ID: 2AVD), tyrosine hydroxylase (PDB ID: 2XSN) proteins. Interrupting critical interactions of the biomolecules can solve the “targeted therapy crisis” problem in neurodegenerative diseases. Since, fisetin can interact with the multi-target proteins involved in the development of Parkinson’s disease, fisetin can be used to design novel and highly efficient drug for the treatment of Parkinson’s disease therapeutics.

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