



MOLECULAR DOCKING OF PLANT FLAVONOIDS: MYRICETIN, QUERCETIN AND KAEMPFEROL, ON HUMAN MAOA AS MULTI-DRUG TARGET TO REDUCE STRESS AND DEPRESSION

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ABSTRACT

MAOA or Monoamine Oxidase A is a flavoenzyme which mediates the breakdown of neurotransmitters, such as dopamine, norepinephrine, and serotonin, via oxidative deamination. It is highly expressed in neural and cardiac cells and is found to be localized on the outer mitochondrial membrane. Serotonin regulates mood, emotion, sleep. Epinephrine and Norepinephrine regulate stress response of our body. Dopamine transmits signal for smooth physical response in our body. Plant alkaloids such as Myricetin, Quercetin and Kaempferol are found in green tea and other fruits and vegetables. Many studies suggest that these flavonoids have an active role in regulation of human emotions, sleep, stress and cognition. The study is aimed to determine the interaction of these flavonoids with MAOA, a molecular target having potential role in stress, cognition and sleep related disorders. Molecular docking was performed to analyze the interaction of these flavonoids on MAOA protein. The structure of the MAOA (2BXR) was extracted from RCSB-Protein Data Bank. Molecular docking was performed using AUTO DOCK 4.0. The docking scores were evaluated by analyzing the minimum binding energy for the first five runs for all the target proteins.

INTRODUCTION

Stress in low amount is good; it keeps you alert, motivated and primed to respond to danger. Yet chronic stress may lead to major depression. Chronic stress leads to secretion of hormone cortisol in elevated level and reduce secretion of neurotransmitters like serotonin, dopamine, epinephrine, norepinephrine. When these neurotransmitters are working normally, they regulate expressions of normal mood, emotions, sleep, appetite, energy level etc [1]. In a difficult situation like death of a loved one,

job loss, divorce, disaster etc., when stress response fails to shut off, it leads to depression in susceptible people [2]. MAOA or monoamine oxidase A is an enzyme secreted by mitochondria in neurons, binds with the neurotransmitter in the synaptic region and stimulate neurodegeneration to stop signal transmission. High levels of MAOA gene has been implicated in many psychological disorders such as Attention Deficit Hyperactivity disorder and major depression disorders, worldwide [1; 3]. MAOA gene is

also involved with panic disorders, bipolar affective disorder, Alzheimer's disease, antisocial behaviour, aggression and Brunner Syndrome (low IQ) [2; 4; 5; 6]. We wanted to identify potential small molecules with anti-MAOA activity. Many cross-sectional studies have shown that drinking green tea is associated with reduction of acute physiological stress and with stress relief [7; 8; 9]. The flavonoids, quercetin, kaempferol and myricetin, are present in adequate amounts in green tea. The main objective of this study was to dock Myricetin, Quercetin and Kaempferol as ligands with the molecular target MAOA (2BXR) protein. *In silico* methods are used in drug designing to help determine drug-target protein interactions. The results obtained from this study would be helpful to understand the mechanism of neuroprotective effect of selected plant flavonoids.

MATERIALS AND METHODS

Drug Likeness

Drug likeness may be defined as a multifaceted combination of various molecular properties and structure characters, which establishes whether a particular small molecule can be a potential drug or non-drug. MolSoft's fingerprints uses a Support Vector Machine (SVM) algorithm to predict overall Drug-likeness score for small molecules [10]. Molecular polar surface area (PSA) and molecular volume are very useful parameter for prediction of drug transport properties, such as intestinal absorption or blood-brain barrier penetration. Volume is therefore often used to model molecular property and biological activity. LogP (octanol /water partition coefficient) is calculated by the methodology developed by Molinspiration. It is a sum of fragment-based contributions and correction factors. The method is very robust and capable of analysing all organic and most organometallic molecules. LogS (water solubility) help to determine transportation feasibility of the drug. MolSoft tool was used to predict the drug likeness of Myricetin, Quercetin and Kaempferol.

Preparation of Protein and ligand: The three dimensional structure of MAOA (2BXR) was

obtained from RCSB protein database. The structural modification was done by removing water molecules, hetatoms and other complex molecules. This is called step helps in proper binding of the ligands to the protein target. Then hydrogen atoms were added to the protein and electronic charges were assigned to the protein using kollman united atoms force field using Autodock tools [11]. Then partial atomic charges were added and possible flexible torsion angles of the ligand was defined. Structure was saved in PDBQT format in Autodock. The 3D structure of ligands, Myricetin, Quercetin and Kaempferol, was drawn by the help of Chems sketch tool [12].

Docking Studies

To understand the molecular interaction of Myricetin, Quercetin and Kaempferol with MAOA, blind docking was performed on MAOA (2BXR) protein. The docking calculation was performed using Genetic Algorithm and Lamarckian Genetic Algorithm. Binding affinity between the 3 ligands and 2BXR target protein was calculated using AutoDock 4.0 [13]. Each of the ligands was docked separately on the target protein. Pre-calculated grid maps on the target protein and ligand were calculated using auxiliary program AutoGrid [14]. The compounds were treated as flexible molecule, with six spatial degrees of freedom for orientation and torsional angles within the gridbox. A free energy forcefield simulation was used to determine the conformation during docking. The binding energy between the ligand and the 2BXR protein depends on the bond stretching; bond bending etc. Therefore the energy of the interaction between two molecules can be calculated in any particular conformation. UCSF Chimera [15] was used to visualize and analyse the docking results.

RESULT AND DISCUSSION

MAOA is a known enzyme involved in depression. As it known that green tea has antidepressant effects. The structure of the green tea flavonoids, Myricetin, Quercetin and Kaempferol are given in **Figure 1, 2, 3**.

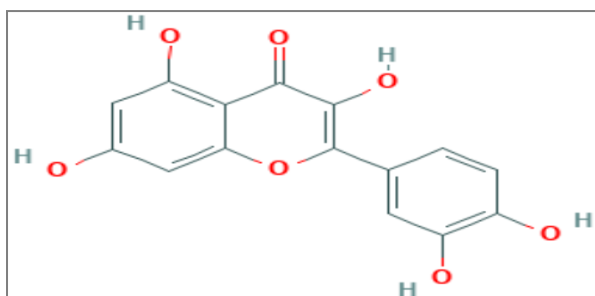


Figure 1: Molecular structure of Quercetin
<https://pubchem.ncbi.nlm.nih.gov/compound/Quercetin#section=2D-Structure>

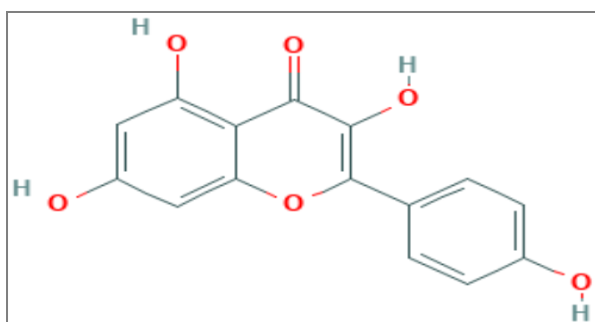


Figure 2: Molecular Structure of Kaempferol
<https://pubchem.ncbi.nlm.nih.gov/compound/5280863#section=2D-Structure>

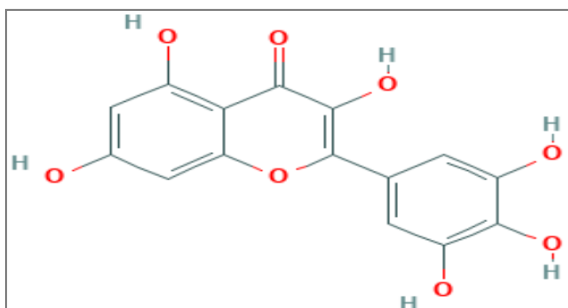


Figure 3: Molecular Structure of Myricetin
<https://pubchem.ncbi.nlm.nih.gov/compound/Myricetin#section=2D-Structure>

SL.No	Minimum binding energy (kcal/mol)	run
1	-8.5	6
2	-8.29	8
3	-8.16	10
4	-8.12	4
5	-7.96	5
6	-7.82	1

Kaempferol : MAO-A

Myricetin: MAO

Sl.No.	Minimum Binding energy (kcal/mol)	run
1	-9.79	9
2	-9.36	6
3	-9.3	8
4	-8.62	10
5	-8.04	4
6	-7.33	7

Sl.no	Minimum binding energy (kcal/mol)	run
1	-9.71	1
2	-8.76	4
3	-8.76	7
4	-8.71	10
5	-7.97	6
6	-6.96	8

Quercetin: MAO-A

Table 1: Minimum Binding Energy of Kaempferol, Myricetin and Quercetin with MAO-A

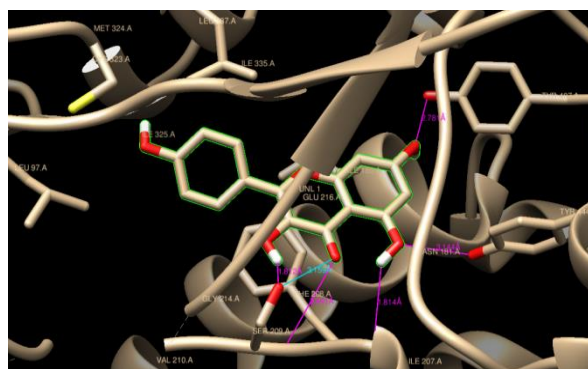


Figure 4: Kaempferol docked on MAO-A

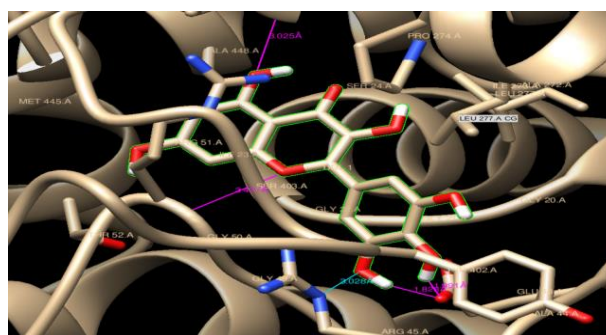


Figure 5: Myricetin docked on MAO-A

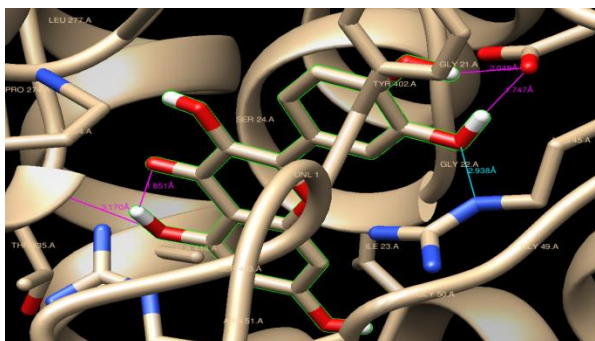


Figure 6: Quercetin docked on MAO-A

Molecular formula: C₁₅ H₁₀ O₇
Molecular weight: 302.04
Number of HBA: 7
Number of HBD: 5
MolLogP : 2.11
MolLogS : -3.87 (in Log(moles/L)) 40.95 (in n
MolPSA : 102.61 A²
MolVol : 281.71 A³
Number of stereo centers: 0

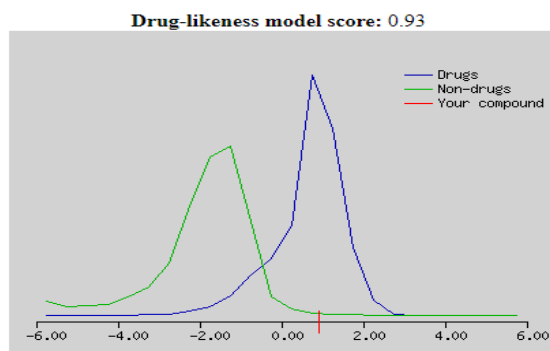


Figure 7: Drug likeliness score of Quercetin

Molecular formula: C₁₅ H₁₀ O₆
Molecular weight: 286.05
Number of HBA: 6
Number of HBD: 4
MolLogP : 2.49
MolLogS : -3.96 (in Log(moles/L)) 31.63 (in mg/L)
MolPSA : 87.13 A²
MolVol : 268.99 A³
Number of stereo centers: 0

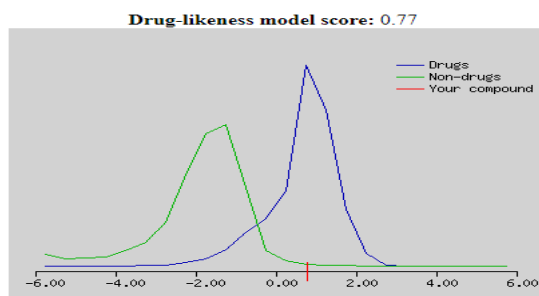


Figure 8: Drug likeliness score of Kaempferol

Molecular formula: C₁₅ H₁₀ O₈
Molecular weight: 318.04
Number of HBA: 8
Number of HBD: 6 (> 5)
MolLogP : 1.73
MolLogS : -3.29 (in Log(moles/L)) 164.52 (in mg/L)
MolPSA : 118.09 A²
MolVol : 292.39 A³
Number of stereo centers: 0

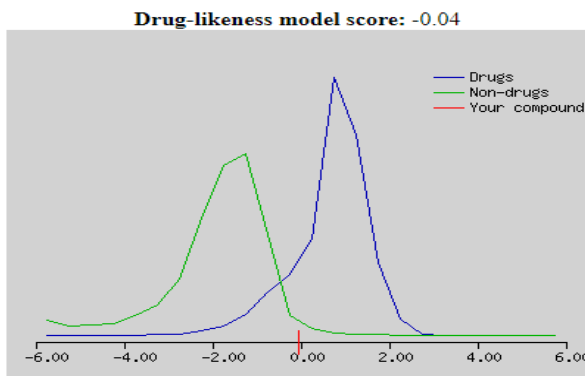


Figure 9: Drug likeliness score of Myricetin

The molecular properties and drug likeliness score for the three flavonoids was calculated using Molsoft (Figure 7, 8, 9). The drug likeliness score of Quercetin is 0.93 (Figure 7) and Kaempferol is 0.77 (Figure 8) and that of Myricetin is 0.04 (Figure 9). Due to high drug likeliness score, we can assume that Quercetin and kaempferol may prove to be a probable drug but not Myricetin as it does not fulfil the properties of being a possible drug molecule. Therefore, Quercetin and Kaempferol could be analysed for their potential antidepressant activity. The interactions, of the three flavonoids with human MAOA, were determined using Autodock 4. The best six minimum binding energy results for the three flavonoids are given in the Table 1. As can be seen, myricetin has the lowest minimum binding energy of -9.79 k cal/mol followed by Quercetin of 9.71 k cal/mol and kaempferol was -8.5 kcal/mol. The minimum energy conformations were chosen and analyzed for viewing the binding and bond formation with MAO using chimera [10]. Figure 4 shows the lowest binding energy conformation of three flavonoids with MAOA. Kaempferol forms 5 hydrogen bonds with active site residues of the enzyme with the bond lengths are 3.144Å, 1.814Å, 3.411Å, 3.159Å; 1.812Å (Figure 4). Figure 5 shows

the lowest binding energy conformation of myricetin with MAOA. It also forms 5 bonds with the enzyme with bond lengths of 3.025Å, 3.427Å, 3.028Å, 1.828Å, 1.991Å. **Figure 6** shows the lowest binding conformation of Quercetin with MAOA. It also forms 5 bonds with the enzyme with bonds lengths of 3.170Å, 1.851Å, 2.938Å, 1.747Å, 2.049Å. The red colour denotes oxygen atom in the ligands and the blue and pink coloured lines denotes the interaction between ligand and the protein molecules.

CONCLUSION

In the present study Monoamine Oxidase A or MAOA (PDB ID: 2BXR) is used as the potential drug target for novel natural drug design. The 3 flavonoids found in green tea, chamomile tea and various fruits and vegetables namely Quercetin, Myricetin and Kaempferol are used as drugs to target the enzyme. According to the drug likeliness comparison among the 3 alkaloids, we found that the drug likeliness score of Myricetin is the lowest being -0.04. Hence, Myricetin possesses the lowest potential of being a drug whereas Quercetin has the highest drug likeliness score of 0.93 hence possesses the highest possibility of being a potential drug for MAOA repression and therefore a possible potential antidepressant. According to the docking studies, Quercetin is involved in hydrogen bond interaction with the highest number of active site residues of MAOA and hence will efficiently bind with the active site with higher specificity than the others. As Quercetin possesses highest drug likeliness score of 0.93 and best binding affinity as predicted by Autodock 4.0, therefore it may prove to be a potential molecule for antidepressant activity obtained from natural sources. Further, experimental studies can be done to prove its role in MAOA inhibitory activity.

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