Research Article

Molecular Docking Studies of Some Flavonoids of Ginkgo biloba with Proteins Probably Responsible for Alzheimer Disease

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Abstract

Alzheimer disease is one of the most common forms of dementia. β-amyloid and tau protein damage in brain is considered to be responsible for this disease. Some flavonoids like Luteolin, Apigenin, Kaemperol, Quercetin, Isorhamnetin, Glycitein, Fustin, Myricetin, Catechin and Rutin are selected for computational theoretical calculations using DFT theory at B3LYP/6-311+G*(d, p) basic set level using Gaussian 16W. The molecular docking investigations are carried out for the same flavonoids using Argus Lab (4.0.1) considering efficient shape-based search algorithm principle and a score function. Ginkgo biloba contains many active ingredients compound like flavonoids and terpenes which are known to slow down Alzheimer disease progression in patients. Binding energies are calculated for all the selected flavonoids with selected proteins. Results show that there is interaction between these flavonoids and selected proteins and this results support to concept of protein kinase binding theory.

Keywords: Alzheimer Disease; Flavonoid; DFT; Molecular Docking; Binding Energies

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Introduction

Alzheimer disease is one of most common form of dementia. Ginkgo biloba leaves extracts are known to slow down Alzheimer's disease (AD) progression in patients. Alzheimer's disease (AD) is a slowly progressive disease of the brain that is characterized by impairment of memory and eventually by disturbances in reasoning, planning, language, perception, reasoning, sensory processing, and conscious thought. According to WHO report, AD will grow nearly 34 million by 2025 and more than 106 million by 2050 and most affected will be seen in the developing countries. So there is immediate need to understand to tackle the life threatening disease. In brain of Alzheimer patients two distinct histological changes are observed in the nerve cells i.e. the formation of extracellular amyloid plaques and intracellular neurofibrillary tangles, so this leads to neurotoxicity. Scientists still are not able to understand what causes AD. But it is clear that this disease develops due of a complex series of events that take place in the brain over a long period of time. Moreover, some other causes include genetic, environmental, and lifestyle factors [1]. Ginkgo is a valuable tree; this tree is found in nearly every country around the globe in urban centers and in temples in Japan and China. Ginkgo biloba has a multitude of phytochemicals, including terpene lactones, biflavones, and flavonoid glycosides, which act on a variety of pathway and receptors [4]. Generally, ginkgo extracts for the preparation of ginkgo products are standardized to contain 24% flavonoids and 6% terpene. Flavonoids and terpene lactones are one of the important parameters to assess the quality of ginkgo products [5]. Flavonoids are found in higher vascular plants, particularly in the flower, leaves and bark. Flavonoids have remarkable antioxidants behavior through various ways including inhibition formation, activity of reactive oxygen species and interaction inhibition with enzymes [6-8].

There are ten types of flavonoids known as Flavones, Flavonols, Flavanones, Flavanonols, Isoflavones, Neoflavonoids, Flavanols or catechins, Anthocyanidins, Chalcones and Biflavones [9-12]. The structural and theoretical study of flavonoids gives great deeper insight into the therapeutic applications. Flavonoids and terpenes are active ingredients of Ginkgo biloba. Ginkgo biloba flavonoids Luteolin, Apigenin, Kaemperol, Quercetin, Isorhamnetin, Glycitein, Fustin, Myricetin, Catechin and Rutin are selected for their docking study with proteins kinase 1iyt - β-amyloid and 1j1c -tau proteins using Argus lab 4.0.1. All the flavonoids were optimizing using DFT theory by B3LYP method at 6-31+G* basis set level in Gaussian 16W software. The aim of present study was to prove that flavonoids can be an appropriate drug molecule to treat Proteins responsible for Alzheimer disease with least side effects and maximum neuroprotective activity.

Material And Methods

Software Gaussian 16w [13], Gauss View 6.0 [14], Argus Lab 4.0.1 [15], were used to study interaction between flavonoids structure in .sdf format [1], and proteins structure in .pdb format [2-3], were saved and retrieved using computer system core i5 with windows 10 as operating system. Whole work required operating Software, window operating system with highly configuration computer system. The three-dimensional crystal structure kinase of β-amyloid and tau proteins with PDB ID : 1j1c [2], and 1iyt [3], where obtained from protein data bank(PDB) online in .pdb format.

Preparation of Three-Dimensional Structure of Target Protein

The three-dimensional structure of β-amyloid and tau proteins kinase 1iyt and 1jlc was obtained from Protein Data Bank, (http://www.rcsb.org/pdb) [2-3]. Macromolecular proteins were separated from the solvent and ligand or non-standard residues. The separation of macromolecules from the unneeded molecules was performed using Argus Lab 4.0.1. [15], and also Protein receptor that had been separated from the residues was optimized. The optimization includes: the addition of hydrogen atoms to macromolecule and setting the grid box parameters. The size of grid box was set at 20 x 20 x 20 (x, y, z) using 0.400000 Å. These results are saved in a format .Agl.

Optimization of Flavonoids

The leaves extract of Ginkgo has more than 40 flavonoids [16]. Ten flavonoids namely Luteolin, Apigenin, Kaemperol, Quercetin, Isorhamnetin, Glycitein, Fustin, Myricetin, Catechin and Rutin were selected for this study. The 3D structure of the flavonoids was downloaded from PubChem(http://PubChem.ncbi.nlm.nih.gov) with .sdf format. The structure of flavonoids was converted and optimized with Gaussian 16W. These results are saved in a format .agl. Various properties of ligands such as logP, molecular weight, H bond donors, H bond acceptors were analyzed. Lipinski's Rule of Five was then applied to select probable flavonoids. DFT method calculations were carried out with the Gaussian 16 package [13], according to Density Functional Theory, using the Becke gradient corrected exchange functional [17], and Lee-Yang-Parr correlation functional [18], with three parameters (B3LYP) [19], method. 6-31+G* basis set was used in gas phase throughout this work. For visualization purpose Gauss view 6 was used to show color of atoms and the charges etc. e.g. atom color code is oxygen (red), carbon (gray) and hydrogen (white) in interaction analysis process [14].

Lipinski's Rule of Five [20] [21]

This rule explains for drug likeness on the base of physical characterization of compounds. According to Lipinski's Rule, out of ten flavonoids only Myricetin, and Rutin do not meets the criteria of Lipinski's Rule, others meet the criteria of rule. The results are displayed in Table 4. Results of Table 4 revealed that Luteolin, Apigenin, Kaemperol, Quercetin, Isorhamnetin, Glycitein, Fustin and Catechin can be clinically and systemically absorbed when administered orally.

Docking and Interaction

Molecular docking is molecular modelling approach which involves the interaction of two or more molecules and provides possibility of stable structure [25]. Commonly utilized docking tools employ search algorithms such as genetic algorithm, fragment-based algorithms, Monte Carlo algorithms and molecular dynamics algorithms. there are some tools such as DOCK, GOLD, FlexX, Argus lab and ICM which are mainly available for high docking simulations. There are various kinds of molecular docking procedures involving either ligand/target flexible or rigid, based upon the objectives of docking simulations [22-23], like flexible ligand docking (target as rigid molecule), rigid body docking (both the target and ligand are rigid molecules) and flexible docking (both interacting molecules as flexible) [24]. Argus lab4.0.1 is the most recent version which has been widely used for virtual screening, due to its enhanced docking speed. In our study we have carried out docking simulation considering flexible ligand docking concepts.

The docking analysis of flavonoids with selected proteins was carried out by using Argus lab 4.0.1. [9], version with involving Gaussian 16W [10], software. The interaction energy between protein and flavonoids were examined from their docking scores [26]. The results of docking calculations are seen in the output were in notepad format.

Results and Discussion

Ginkgo biloba is exceptionally known for many characteristics that make it extremely valuable socially, medically, historically, and economically. Molecular docking is an analysis method to predict the binding orientation of small ligand molecule to their protein binding targets.

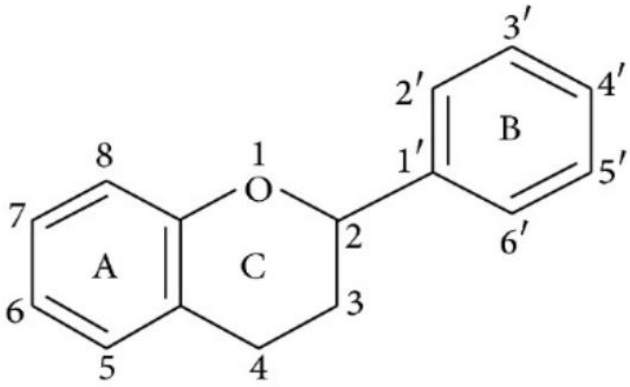
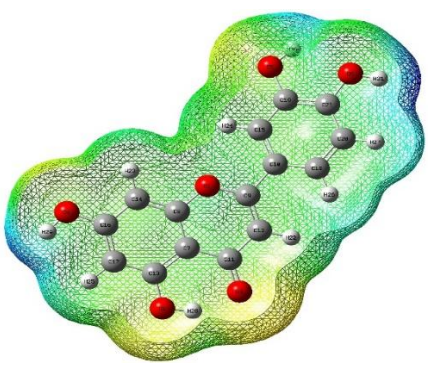


Figure 1 Basic Structure of Flavonoids

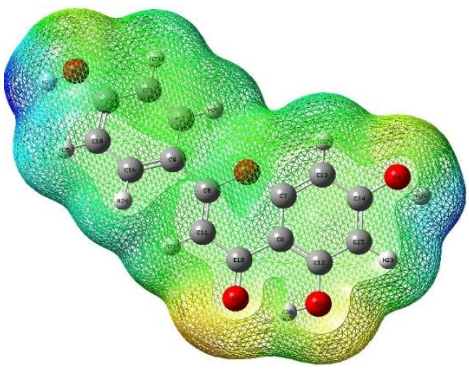
Table 1 Details of Flavonoids Selected for Docking Study

Flavonoids	Compounds name	3	5	7	3'	4'	5'
Flavones	Luteolin	H	OH	OH	OH	OH	H
	Apigenin	H	OH	OH	H	OH	H
Flavonols	Kaempferol	OH	OH	OH	H	OH	H
	Quercetin	OH	OH	OH	OH	OH	H
	Myricetin	OH	OH	OH	OH	OH	OH
	Isorhamnetin	OH	OH	OH	H	OH	OCH_3
	Rutin	H	OH	OH	OH	OH	H
	Fustin	OH	H	OH	H	OH	OH
Isoflavones	Glycitein	H	H	OH	H	OH	H
Flavanols	Catechin	OH	OH	OH	H	OH	OH

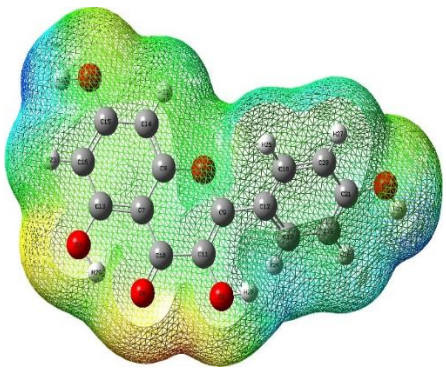
OH (3,5,7,3',4',5') position in flavonoid structure decides the activity in flavonoids. On the basis of OH its category of flavonoid is decides and it also depend on position of ring. Here we studied four categories of flavonoids are selected and in total ten different flavonoids. Hydrogen bonding between hydroxyl groups in A and C rings is not affected by the presence of hydroxyl groups in B-ring. the molecular planarity of the studied molecules is forced by the presence of 3-OH group through the development of a hydrogen bonding with 6'-H atom in catechol B-ring. Structural optimizations were carried out for 10 derived flavonoids with the calculated structures and its MESP (molecular electrostatic potential) images were reported which shown in **Figure 2**. In table of Figures 2, Figure 2a of Luteolin, Figure 2b of Apigenin, Figure 2c of Kaemperol, Figure 2d of Quercetin, Figure 2e of Myricetin, Figure 2f of Isorhamnetin, Figure 2g of Rutin, Figure 2h of Fustin, Figure2i of Glycitein, and Figure 2j of Catechin and the main molecular parameters are given in **Table 2** and **Table 4**.



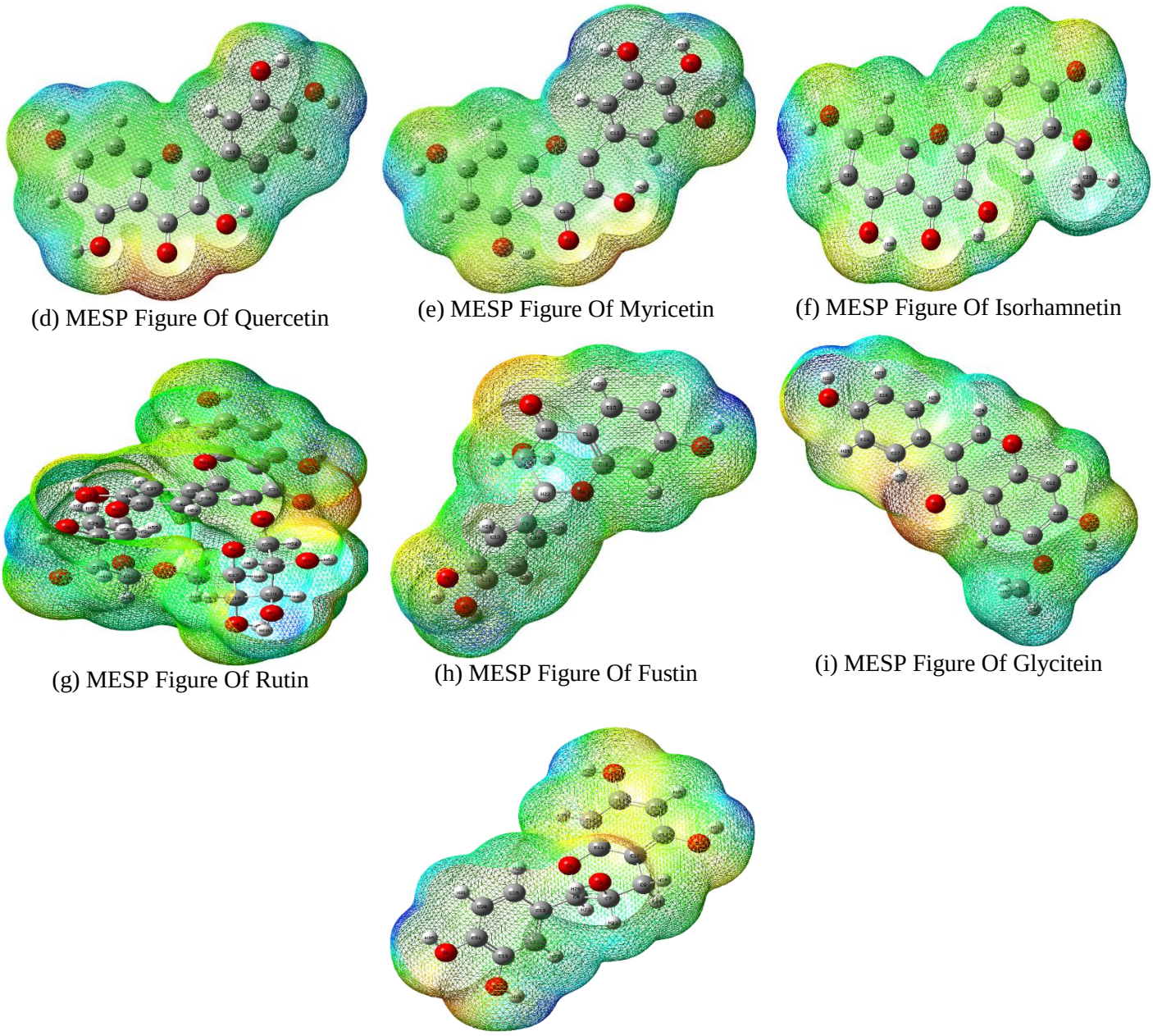
(a) MESP Figure Of Luteolin



(b) MESP Figure Of Apigenin



(c) MESP Figure Of Kaempferol



(d) MESP Figure Of Quercetin (e) MESP Figure Of Myricetin (f) MESP Figure Of Isorhamnetin

(g) MESP Figure Of Rutin (h) MESP Figure Of Fustin (i) MESP Figure Of Glycitein

(j) MESP Figure Of Catechin

Figure 2 MESP (Molecular Electrostatic Potential) Figures of Flavonoids Using B3LYP/6-311+G* Level (Red Color Indicating Highly Negative Charge and Blue Color Indicating Highly Positive Charge)

According to parameters of Lipinski rule of 5 that logP is not greater than 5, molecular mass less than 500 gm/mol, H-Bond donor not more than 5, H-Bond accepter not more than 10 and polar surface area not greater than 140 $A^{\circ 2}$. From Table 4 it is clear that the 8 out of 10 ligands follow the rule and show good drug likeness.

The selected Flavonoids followed flexible ligand docking process when dock with active site of the β-amyloid and tau proteins. In the binding pocket interactions, first all water molecules are removed from proteins, then hydrogens were added. The common H-bonding interactions were formed between all docked flavonoids with amino acid residues 21ALA, 23ASP, 22GLU, 25GLY, 17LEU, 16LYS, 19PHE, 20PHE, 18VAL, and 24VAL for β-amyloid and residues of chain B 583ALA, 564ASN, 686ASN, 633ASP, 700ASP, 685GLN, 563GLY, 565GLY, 562ILE, 632LEU, 688LEU, 585LYS, 567PHE, 638THR, 634TYR, 570VAL, 610VAL, 635VAL and 931MG for tau protein. This revealed that the flavonoids can frequently interact with amino residues binding site and that these residues are responsible for the selectivity of flavonoid inhibitors.

Table 2 Geometrical and Energetic Parameters of Optimized Flavonoids in Gas Phase Calculated at B3LYP/6-311+G* Level. (Atom Numbering of Atom Is Same as Given You in **Figure 1**)

Flavonoids	Compounds Name	Interatomic Distance r in Angstrom(A°)							E a.u.	μ in D
		(C4=O)	(3-OH)	(5-OH)	(7-OH)	(3'-OH)	(4'-OH)	(5'-OH)		
Flavones	Luteolin	1.2559	-	0.9999	0.9666	0.9691	0.9658	-	-1029.03397905	5.0372
	Apigenin	1.2392	-	0.9988	0.9666	-	0.9658	-	-2179.75762225	4.3756
Flavonols	Kaempferol	1.2508	0.9683	0.9988	0.9666	-	0.9666	-	-1028.86163358	4.9772
	Quercetin	1.2272	0.9685	0.9672	0.9665	0.9693	0.9657	-	-1104.07107679	6.3824
	Myricetin	1.2503	0.9689	0.9989	0.9666	0.9658	0.9696	0.9691	-1179.29469882	7.0016
	Isorhamnetin	1.2646	0.9804	0.9914	0.9666	-	0.9706	OCH_3	-1143.41812930	0.9565
	Rutin	1.2365	-	0.9670	0.9662	0.9794	0.9724	-	-2249.75224783	9.4637
	Fustin	1.2236	0.9683	-	0.9667	-	0.9654	0.9691	-1030.21236988	4.8144
Isoflavones	Glycitein	1.2353	-	-	0.9709	-	0.9662	-	-992.975532187	2.1729
Flavanols	Catechin	-	0.9685	0.9659	0.9660	-	0.9662	0.9661	-1031.32945972	1.1115

Table 3 Mullikan Charge Values Calculated On Various Atom for Various Flavonoids in Gas Phase Calculated at B3LYP/6-311+G* Theoretical Level

	Flavones				Flavonols								Isoflavones		Flavanols	
	Luteolin		Apigenin		Kaempferol		Quercetin		Myricetin		Isorhamnetin		Rutin		Fustin		Glycitein		Catechin	
1	O	-0.325388	O	-0.332784	O	-0.352806	C	-0.292621	O	-0.352366	O	-0.381809	O	-0.164677	O	-0.286901	O	-0.330947	O	-0.200611
2	O	-0.558231	O	-0.558008	O	-0.527452	O	-0.487842	O	-0.519859	O	-0.599945	O	-0.253747	O	-0.406794	O	-0.465961	O	-0.474666
3	O	-0.601415	O	-0.601715	O	-0.558424	C	1.613732	O	-0.557231	O	-0.542608	O	-0.313672	O	-0.469653	O	-0.531943	O	-0.533697
4	O	-0.506283	O	-0.506843	O	-0.567156	C	0.207298	O	-0.564974	O	-0.456499	O	-0.510935	O	-0.540360	O	-0.523502	O	-0.528451
5	O	-0.542114	O	-0.506599	O	-0.508942	C	-0.869875	O	-0.509230	O	-0.669318	O	-0.445954	O	-0.504524	O	-0.517241	O	-0.518570
6	O	-0.595843	C	1.584810	O	-0.507176	C	0.036066	O	-0.609995	O	-0.501483	O	-0.257745	O	-0.605513	C	1.297546	O	-0.520271
7	C	1.578249	C	-0.504565	C	1.725571	O	-0.517711	O	-0.536098	O	-0.535301	O	-0.422624	C	-0.128751	C	0.494566	C	-0.155037
8	C	-0.495760	C	0.705048	C	-0.885242	C	0.510941	O	-0.600742	C	1.684428	O	-0.469882	C	-0.102157	C	-1.248843	C	-0.111855
9	C	0.593471	C	0.747001	C	0.656264	O	-0.350664	C	1.748558	C	0.794446	O	-0.609169	C	0.667730	C	0.014953	C	-0.057180
10	C	0.819219	C	-0.553296	C	-0.521002	C	-0.346964	C	0.521200	C	-0.700886	O	-0.416401	C	0.290014	C	0.612298	C	1.228961
11	C	-0.531090	C	-0.393597	C	0.233752	O	-0.468638	C	-0.920815	C	1.104723	O	-0.236343	C	0.752264	C	-0.104206	C	-1.691663
12	C	-0.414469	C	-0.247952	C	0.402534	C	0.331463	C	0.613160	C	-0.149346	O	-0.46473	C	-1.259947	C	-0.212299	C	0.180093
13	C	-0.247689	C	-0.498178	C	-0.260610	C	0.416943	C	0.158420	C	-0.422220	O	-0.470854	C	-1.089104	C	0.435253	C	0.344247
14	C	-0.483643	C	-0.373905	C	-0.353537	C	-0.415433	C	-0.485925	C	-0.777206	O	-0.505148	C	0.111526	C	-0.135144	C	-0.357125
15	C	-0.586297	C	0.654263	C	-0.278554	C	-0.350415	C	-0.290108	C	-0.422865	O	-0.611438	C	-0.330695	C	-0.161518	C	-1.166289
16	C	-0.367137	C	-0.543178	C	0.548596	C	-0.696237	C	-0.347442	C	-0.598487	O	-0.512359	C	0.294059	C	-0.653978	C	0.125935
17	C	0.634951	C	-0.627648	C	-0.704172	O	-0.517834	C	-0.517685	C	0.024703	C	0.141675	C	0.395503	C	-0.367152	C	0.879049
18	C	-0.483005	C	0.303074	C	-0.480266	C	0.422835	C	-0.463637	C	-0.348044	C	-0.187894	C	-0.233143	C	0.237493	C	-0.346200
19	C	0.469647	C	0.480502	C	0.411711	C	0.19545	C	-0.296486	C	0.942715	C	0.041513	C	0.602758	C	0.417903	C	0.545015
20	C	0.050970	C	-0.316705	C	0.508243	O	-0.539473	C	0.588753	C	-0.051143	C	0.003184	C	-0.020351	C	-0.304460	C	-0.024060
21	C	0.219655	H	0.140335	C	-0.312259	C	0.199558	C	0.394654	C	0.065324	C	-0.168907	C	0.286375	C	-0.131132	C	0.409778
22	H	0.141523	H	0.142612	H	0.142963	O	-0.599261	C	0.211132	C	-0.085736	C	0.011388	H	0.138599	H	0.161258	H	0.114832

H	0.144640	H	0.124391	H	0.124402	H	0.351964	C	0.464143	C	-0.130292	C	-0.071325	H	0.154005	H	0.150897	H	0.121976
H	0.155175	H	0.131682	H	0.154097	H	0.120052	H	0.140287	H	0.143977	C	-0.055455	H	0.128750	H	0.147701	H	0.156947
H	0.124295	H	0.147061	H	0.146027	H	0.374999	H	0.161915	H	0.148271	C	-0.418939	H	0.129627	H	0.118065	H	0.182186
H	0.129581	H	0.117108	H	0.119123	H	0.119699	H	0.126398	H	0.137633	C	-0.13936	H	0.166553	H	0.145090	H	0.110503
H	0.120147	H	0.142040	H	0.143967	H	0.149857	H	0.124617	H	0.125509	C	0.341469	H	0.148655	H	0.107188	H	0.098884
H	0.423278	H	0.423495	H	0.356959	H	0.15103	H	0.356599	H	0.140973	C	-0.59678	H	0.352675	H	0.134775	H	0.353127
H	0.363567	H	0.363767	H	0.422993	H	0.362432	H	0.423347	H	0.419817	C	-0.007991	H	0.116705	H	0.396371	H	0.151894
H	0.390521	H	0.357784	H	0.362922	H	0.120798	H	0.363278	H	0.423956	C	-0.594527	H	0.113835	H	0.151926	H	0.113892
H	0.379476			H	0.357473	H	0.389055	H	0.383564	H	0.364826	C	0.732147	H	0.389778	H	0.157026	H	0.113229
						H	0.378799	H	0.389220	H	0.392341	C	1.287092	H	0.361606	H	0.156789	H	0.370290
						C	-0.292621	H	0.403349	H	0.154915	C	0.423935	H	0.376876	H	0.351228	H	0.357454
										H	0.154918	C	-0.88015					H	0.363997
										H	0.149712	C	-0.04898					H	0.363387
												C	-0.170486						
												C	-0.357484						
												C	-0.130732						
												C	0.552089						
												C	-0.361896						
												C	0.165281						
												C	0.022461						
												C	0.512888						

Table 4 Docking Data on Interaction of Flavonoids with Selected Proteins

Sr. No	Flavonoids	M.F.	M.W. (gm/mol)	TPSA	LogP	Number of Atoms	H-Bond accepter	H-Bond donor	Number of Electrons	Docking Score with B-amyloid Kinase- 1iyt (kcal/mole)	Docking Score with Tau Protein Kinase- 1j1c (kcal/mole)
1	Luteolin	$C_{15}H_{10}O_6$	286.239	107 A^{o2}	1.4	31	6	4	148	-8.19645	-9.93891
2	Apigenin	$C_{15}H_{10}O_5$	270.240	87 A^{o2}	1.7	66	5	3	260	-7.71174	-8.88009
3	Kaempferol	$C_{15}H_{10}O_6$	286.239	107 A^{o2}	1.9	31	6	4	148	-8.29863	-8.40885
4	Quercetin	$C_{15}H_{10}O_7$	302.238	127 A^{o2}	1.5	32	7	5	156	-7.92728	**NA**
5	Myricetin	$C_{15}H_{10}O_8$	318.237	148 A^{o2}	1.4	33	8	6	164	-7.86168	-7.96502
6	Isorhamnetin	$C_{16}H_{12}O_7$	316.265	116 A^{o2}	1.9	35	7	4	164	-7.31572	-8.27665
7	Rutin	$C_{27}H_{30}O_{16}$	610.521	266 A^{o2}	-1.3	73	16	10	320	**NA**	-7.94826
8	Fustin	$C_{15}H_{12}O_6$	288.255	107 A^{o2}	1.3	33	6	4	150	-8.02798	-9.96737
9	Glycitein	$C_{16}H_{12}O_5$	284.267	76 A^{o2}	2.4	33	5	2	148	-8.20050	-8.66665
10	Catechin	$C_{15}H_{14}O_6$	290.271	110 A^{o2}	0.4	35	6	5	152	-8.06252	-8.74001

- NA- Not Acceptable Pose Was Calculated (No Binding Occur)

The calculated flavonoids atom bond length, energy and dipole moments are in the Table 2. Data show that the interatomic O-H distances are in following order 5-**OH > 3-OH > 3'-OH, 4'-OH, 5'-OH** and distances for 3'-OH, 4'-OH, 5'-OH are almost equal to those for 7-OH. Data in table shows that as position of 3'-OH increase with dipole moment of molecules because polarity of molecules was increases.

From Table 3, it can be seen that the oxygen atom of flavonoids at position 4 has higher negative electrostatic potential because Mullikan charge value lies between -0.48 to -0.66 and the C-atom nearest to oxygen has higher positive Mullikan charge value between 0.66 and 1.74. The O(oxygen) atom of the phenolic group also shows high negative electrostatic potential and H-atom of the phenolic –OH group show higher positive electrostatic potential so intermolecular interactions like formation of new H-bond and noncovalent interactions are possible in these molecules. On the basis of optimized structures of flavonoids MESP (molecular electrostatic potential) images are generated, which table is shown in Figure 2a-j. In every image, oxygen atom of keto group shows negative electrostatic potential so there is maximum chance of binding with proteins.

The main objective of molecular docking is to attain ligand-receptor complex with optimized conformation and with the intention of possessing less binding free energy. The net predicted binding free energy (ΔG_{bind}) is revealed in terms of various parameters, hydrogen bond (ΔG_{hbond}), electrostatic (ΔG_{elec}), torsional free energy (ΔG_{tor}), dispersion and repulsion (ΔG_{vdw}), desolvation (ΔG_{desolv}), total internal energy (ΔG_{total}) and unbound system's energy (ΔG_{unb}). Therefore, good understanding of the general ethics that govern predicted binding free energy (ΔG_{bind}) provides additional clues about the nature of various kinds of interactions leading to the molecular docking. [23]

$$\Delta G_{bind} = (\Delta G_{hbond} + \Delta G_{elec} + \Delta G_{tor} + \Delta G_{vdw}) + \Delta G_{desolv} + \Delta G_{total} - \Delta G_{unb} \quad (1)$$

Lowest ΔG_{bind} decides the binding characterization of a compound. Low ΔG_{bind} energy indicates that the conformations formed are stable, whereas high ΔG_{bind} energy indicates that less stable binding is formed. From results given in Table 4 flavonoids showed binding energy in the range -7.3 kcal/mol to -8.2 kcal/mol with β-amyloid Protein Kinase (PDB ID: 1iyt) and –7.9 kcal/mol to -9.9 kcal/mol with Tau Protein Kinase (PDB ID: 1j1c). Kaempferol produced the lowest value than other flavonoids with β-amyloid Protein and fustin produced the lowest value than other flavonoids with Tau Protein. This proves that flavonoids are potential neuroprotective agents. Results of Table 4 shows that the protein residues that interact with the ligand. Hydrogen bond and hydrophobic contacts play an important role in the interaction between the flavonoids and the target protein. The best possible binding mode of the flavonoids with target protein is shown in **Figure 3** for β-amyloid Protein Kinase (PDB ID: 1iyt) interaction of docking and **Figure 4** for Tau Protein Kinase (PDB ID: 1j1c) interaction of docking. For validating, the protein was redocked with already bound flavonoids. The docking score (or G score) of flavonoids was found to be negative, thus it is considered β-amyloid Protein Kinase -1iyt and Tau Protein Kinase - 1j1c as fair docking score.

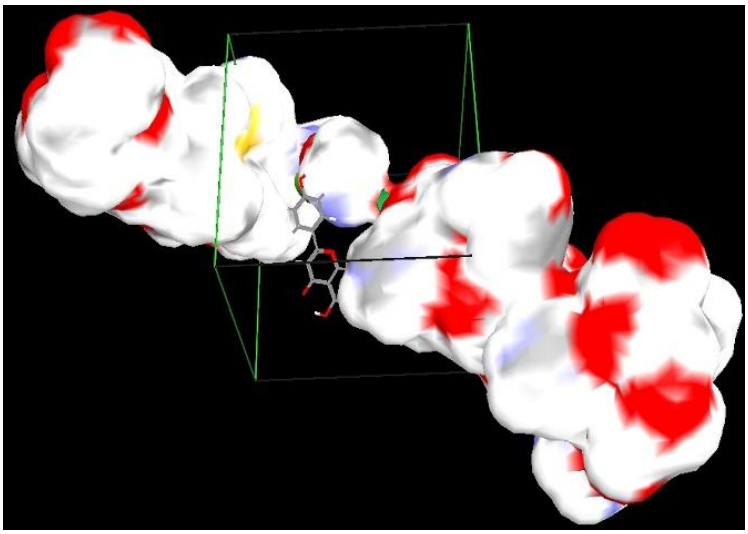


Figure 3 B-Amyloid Protein Kinase (PDB ID: 1iyt) Interaction of Docking

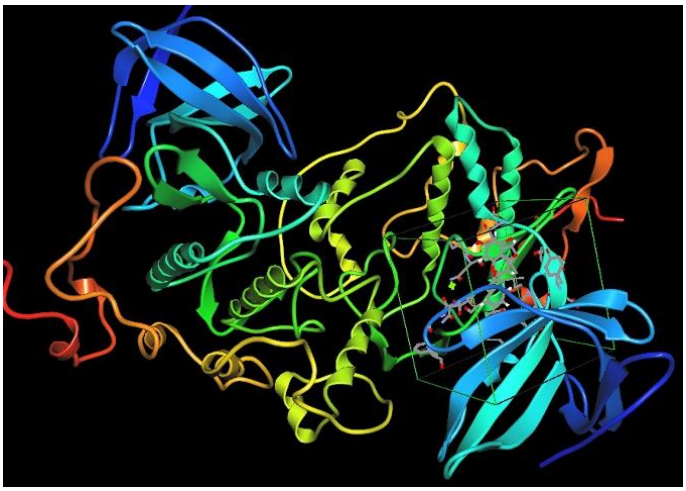


Figure 4 Tau Protein Kinase (PDB ID: 1j1c) Interaction of Docking

Conclusion

Here, Insilico docking screening using automated docking concepts was use to find flavonoids as neuroprotective candidates for treating Alzheimer disease. All the selected flavonoids showed binding energy ranging between -7.3 kcal/mol to -8.2 kcal/mol with β-amyloid Protein Kinase (PDB ID: 1iyt) and binding energy ranging between –7.9 kcal/mol to –9.9 kcal/mol with Tau Protein Kinase (PDB ID: 1j1c). From the docking approach using Argus lab considering docking strategy and docking scores, flavonoids can interact with proteins responsible for Alzheimer disease. So flavonoids can be used to treat Alzheimer disease as neuroprotection and it can reduce the further progression in the body.

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References

[1] S. Gupta, A. Pandey, A. Tyagi, G. Mohan, Computational Analysis of Alzheimer's Disease Drug Targets, Curr. Res. Inf. Pharm. Sci. 11 (2010).
[2] https://www.rcsb.org/structure/1j1c
[3] https://www.rcsb.org/structure/1iyt
[4] C. Ude, M. Schubert-Zsilavecz, M. Wurglics, Ginkgo biloba extracts: A review of the pharmacokinetics of the active ingredients, Clin. Pharmacokinet. 52 (2013) 727–749. doi:10.1007/s40262-013-0074-5.
[5] J. Kleijnen, P. Knipschild, Ginkgo biloba, Lancet. 340 (1992) 1136–1139. doi:10.1016/0140-6736(92)93158-J.
[6] Jovanovic, S.V.; Steenken, S.; Tosic, M.; Marjanovic, B.; Simic, M.G. Flavonoids as antioxidants. J. Am. Chem. Soc. 1994, 116, 4846–4851.
[7] Cotelle, N. Role of flavonoids in oxidative stress. Curr. Top. Med. Chem. 2001, 1, 569-590.
[8] Nagao, A.; Seki, M.; Kobayashi, H. Inhibition of xanthine oxidades by flavonoids. Biotechnol. Biochem. 1994, 63, 1787–1790.
[9] Rosa L.A., Alvarez-Parrilla E., Gonzàlez-Aguilar G.A. Fruit and vegetable phytochemicals: chemistry, nutritional value, and stability. 1th Edition. Wiley J. & Sons, Inc., Publication, 2010
[10] Han X., Shen T. and Lou H. Dietary polyphenols and their biological significance. Int J Mol Sci 2007;9:950-988. doi:10.3390/i8090950
[11] Manach C., Scalbert A., Morand C., Rémésy C., and Jime´nez L. Polyphenols: food sources and bioavailability. Am J Clin Nutr 2004;79(5):727-47 [Abstract]
[12] Tsao R. Chemistry and biochemistry of dietary polyphenols. Nutrients 2010;2:1231-1246. doi:10.3390/nu2121231
[13] Gaussian 16, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L.

Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

[14] GaussView, Version 6, Roy Dennington, Todd A. Keith, and John M. Millam, Semichem Inc., Shawnee Mission, KS, 2016.

[15] Thompson, M. A., Molecular docking using ArgusLab, an efficient shape-based search algorithm and the AScore scoring function. ACS meeting, Philadelphia, 172, CINF 42, PA. (2004).

[16] T. Hori. R.W. Ridge· W. Tulecke, P. Del Tredici. J. Tremouillaux-Gui1ler, H. Tobe (Eds.) Ginkgo Biloba A Global Treasure From Biology to Medicine

[17] Becke, A.D. Density-functional exchange-energy approximation with correct asymptotic behavior. Phys. Rev. A 1988, 38, 3098–3100

[18] Lee, C.; Yang, W.; Parr, R.G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. Phys. Rev. B 1988, 37, 785–789.

[19] Becke, A.D. Density-functional thermochemistry. III. The role of exact exchange. J. Chem. Phys.1993, 98, 5648–5652.

[20] Lipinski CA, Lombardo F, Dominy BW, Feeney PJ (March 2001). "Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings". Adv. Drug Deliv. Rev. 46 (1-3): 3–26. doi:10.1016/S0169-409X(00)001,

[21] Lipinski CA (December 2004). "Lead- and drug-like compounds: the rule-of-five revolution". Drug Discovery Today: Technologies. 1 (4): 337–341. doi:10.1016/j.ddtec.2004.11.007,

[22] Lamb ML, Jorgensen WL (1997) Computational approaches to molecular recognition. Curr Opin Chem Biol 1: 449-457.

[23] Gschwend DA, Good AC, Kuntz ID (1996) Molecular docking towards drug discovery. J Mol Recognit 9: 175-186.

[24] Dar AM, Mir S (2017) Molecular Docking: Approaches, Types, Applications and Basic Challenges. J Anal Bioanal Tech 8: 356. doi: 10.4172/2155-9872.1000356

[25] A. Madeswaran, M. Umamaheswari, K. Asokkumar, T. Sivashanmugam, V. Subhadradevi, P. Jagannath, Computational drug discovery of potential tau protein kinase i inhibitors using in silico docking studies, Bangladesh J. Pharmacol. 8 (2013) 131–135. doi:10.3329/bjp.v8i2.13886.

[26] Agarwal S, Chadha D, Mehrotra R (2015) Molecular modeling and spectroscopic studies of semustine binding with DNA and its comparison with lomustine–DNA adduct formation. J Biomol Struct Dyn 33: 1653-1668.

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