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Computational analysis of nutrients in Parkinson's

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ABSTRACT
4-hydroxybenzoic acid, a monohydroxybenzoic acid, Ferulic acid (FA), is one of the phenolic acids are commonly found in medicinal plants and known for their efficacy in numerous diseased conditions. The present study was based on the computational assessment of 4-Hydroxy benzoic acid, ferulic acid, and p-coumarin as possible neuroprotective agents in Parkinson's disease. Docking and simulation assays were used for 4-Hydroxybenzoic acid, ferulic acid and p-Coumaric acid (procured from Merck India Ltd). HyperChem software was used in molecular remodelling. Schrodinger® docking suits (Version 11.9.011, Platform Windows-x64) were used to perform molecular docking calculations through a virtual screening approach. This process made use of enhanced precision XP. Using the force field OPLS4, protein was generated through restricted minimization. A Glide® receptor grid generator with a docking length of 20Å was used to construct the grid sites. The bioavailability score was estimated constant as 0.85 in 4-hydroxybenzoicacid, ferulic acid and p-coumaric acid compounds. They all followed Lipinski rule. For AKT1 target site, the docking (energy) score was obtained as -5.031kcal/mol, -5.959kcal/mol and -5.193kcal/mol in 135, 445858 and 637542 compounds, respectively. For M1, 3 docking structures were drawn with different energy score was observed as -7.215kcal/mol, -7.199kcal/mol, and -7.064kcal/mol, in PBD ID 1008. In conclusion, 4-Hydroxybenzoic acid, ferulic acid and p-coumaric acid exhibited the bioavailability score of 0.85 and followed the Lipinski rule. All the compounds demonstrated almost similar docking score against all the target sites in Parkinson's disease. Among all the PBD ID i.e., 1008, 4DJU, and 1Q5K, maximum energy score was found in PBD ID 1008 that exhibited a significant docking profile of M1, M2 and M3. It suggests that 4-Hydroxybenzoic acid, ferulic acid and p-coumaric acid showed neuroprotective effect that might be possibly effective in the management of Parkinson's disease (PD) and other neurological problems.

Keywords: Neuroprotective, 4-Hydroxy benzoic acid, ferulic acid, p-coumarin, docking study

INTRODUCTION

"Parkinson's disease" (PD) was initially described by J. Parkinson in 1817 "Essay on the Shaking Palsy" [1]. It is characterised by a variety of motor and non-motor symptoms, as well as the hallmark symptoms of rigidity, postural instability, bradykinesia, and rest tremor [2,3]. As the world's population ages and lives longer, age-related illnesses like Parkinson's disease are drawing more attention from sci. PD is the neurological condition with the quickest rate of growth. Neurological disorders are currently the primary cause of disability worldwide [4]. It is predicted that PD patients will be approximately 13 million by 2040 [5]. Two significant discoveries in the etiopathogenesis of PD include the finding by Frederick Lewy in 1912 of intracytoplasmic inclusion bodies, or "Lewy bodies," as a pathologic signature and the discovery of dopamine insufficiency and its role in parkinsonian animal models [6].

It has been disputed how much of a role genes and environmental/lifestyle variables have in the pathophysiology of Parkinson's disease. The 60 years is the onset age for PD [7,8]. The incidence may be impacted by various factor i.e., cigarette-smoking, postmenopausal hormone use, and caffeine use. It is prone in men than in women [9,10]. Numerous risk factors have been linked to the disease, such as exposure to pesticides and heavy metals, living in rural areas, working in agriculture, having a traumatic brain injury, having a history of melanoma,

consuming dairy products, having type 2 diabetes (which can be controlled with the use of antidiabetic medications), and many more [7].

Coumarins are a class of chemical compounds with both natural and synthetic origins that are among the promising natural compounds in human health [11]. For over 200 years, coumarins have been the subject of research. More than 60 plants contain the semi-volatile lactone, 1,2-benzopyrone, also known as coumarin 2H-chromen-2-one. It has a pleasant smell. The various coumarin derivatives have unique qualities that enable them to have a variety of therapeutic effects and, consequently, numerous applications in various medical fields, demonstrating their utility as biomarkers, anti-HIV, anticoagulant, anti-neoplastic, carbonic anhydrase blockers, and anti-inflammatory [12,13]. The resistance that some medications cause when taken is one of the primary reasons that the biosynthesis of coumarin derivatives has turned to, which has become a major hindrance to the growth and management of various cancer kinds. This has led to the development of naturally occurring substances and some synthetic molecules that evaluate potential resistance during administration and have shown a great deal of efficacy in preventing multidrug resistance (MDR) in cancer patients [14]. The oxidative processes of coumarins are induced by cytochrome P450 in hepatic metabolism, as demonstrated by coumarins. Additionally, it has been shown that the gut microbiota is significant. Rapid absorption causes coumarins to be dispersed throughout the body, with the liver and kidneys containing the highest quantities. It is unknown if oral consumption causes a significant buildup of coumarin or its metabolites in the tissues. The mode of elimination is contingent upon the coumarin type and mode of administration [15].

Ferulic acid (FA) is one of the phenolic acids that are frequently found in medicinal plants. FA is primarily found in plant cell walls, where it forms covalent bonds with polysaccharides like arabinoxylans, a precursor to lignin, a complex polymer that gives plant tissues mechanical strength and resistance to biodegradation [16,17]. This linkage helps to maintain the structural integrity and rigidity of the plant cell walls. FA and its derivatives have been shown to have a range of pharmacological actions thus far, with particular emphasis on anti-oxidative, anti-inflammatory, anti-allergic, anti-cancer, and anti-fibrotic properties [18].

4-hydroxybenzoic acid is a monohydroxybenzoic acid. It is a white, crystalline substance that dissolves more readily in polar organic solvents like acetone and alcohols than it does in water or chloroform [19]. The main function of hydroxybenzoic acid is as the starting point for the synthesis of its esters, or parabens, which are employed as preservatives in several ophthalmic solutions and cosmetics [20]. It is isomeric with 3-hydroxybenzoic acid and 2-hydroxybenzoic acid, also referred to as salicylic acid and a precursor to aspirin. 4-Hydroxybenzoic acid's low toxicity makes it a well-liked antioxidant. In mice, the LD50 is 2200 mg/kg (oral). 4-Hydroxybenzoic acid increases the development of human breast cancer cell lines and has estrogenic action both in vitro and in vivo. It is a typical metabolite of esters of parabens, like methylparaben [21].

1. MATERIALS AND METHODS

Chemicals and software

4-Hydroxybenzoicacid, ferulic acid and p-Coumaric acid were obtained from the Merck India Ltd. HyperChem software, Schrodinger Maestro, (M M Share Version 4.5.011) software was used in molecular remodelling, docking and simulation studies.

Molecular remodelling

HyperChem was used to draw all of the structures, and clean molecular graphing in 3 dimensions and the molecular mechanics MM+ force field were used to minimise the structures' molecular geometries. No limits were placed on the conversion of aromatic forms. Following 100 cycles of optimisation, a random search strategy with 1000 interactions, the 10 lowest minimal energy conformers, and the optimised structures were subjected to conformational analysis. The MOL format was used to store the compounds.

Molecular Docking

Molecular docking calculations were completed using Schrodinger® docking suits (Schrödinger Maestro, Version 11.9.011, Platform Windows-x64) using a virtual screening workflow. This workflow utilized extra precision XP. Protein was prepared by restrained minimization using force field OPLS4. The grid sites were created using a Glide® receptor grid generator with a docking length of 20Å. Grid centres were determined from active residues on the target protein. The essential phytoconstituents' three-dimensional conformer structure was downloaded as an SDF file from the PubChem database. Ligands were prepared using force field OPLS4 and possible states were generated from pH 7.0±2.0. The possibility of spontaneous binding between the receptor and ligand was demonstrated by a negative docking score (in kcal/mol) the more negative the number, the better binding. Excellent binding activity between the receptor and ligand was shown by a docking score of less than -5 kcal/mol. PyMOL 2.4.0 were used to illustrate the results demonstrating increased activity and obtaining 3D and 2D diagrams of docked target-ligand complex respectively.

Table 1. Ligand information for molecular docking

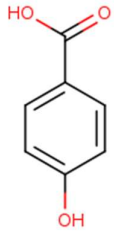
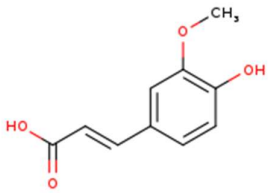
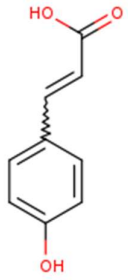
Compound	4-Hydroxybenzoic acid	Ferulic acid	p-Coumaric acid
CID	135	445858	637542

RESULTS AND DISCUSSION

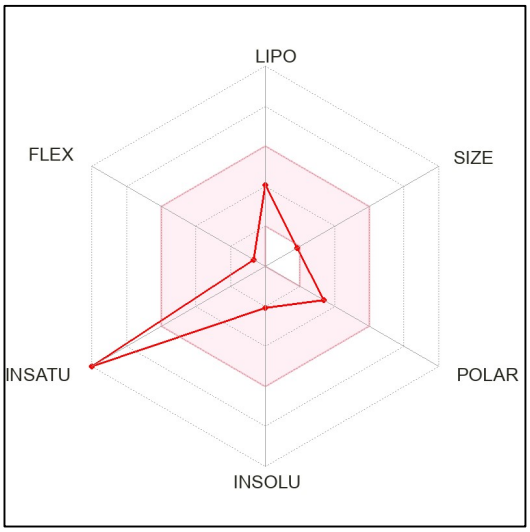
Molecular remodelling

The molecular modelling of different compounds i.e., 4-hydroxybenzoic acid, ferulic acid and p-coumaric acid, was performed as shown in below table. The bioavailability score was estimated constant as 0.85 in 4-hydroxybenzoic acid, ferulic acid and p-coumaric acid compounds. They all followed Lipinski rule.

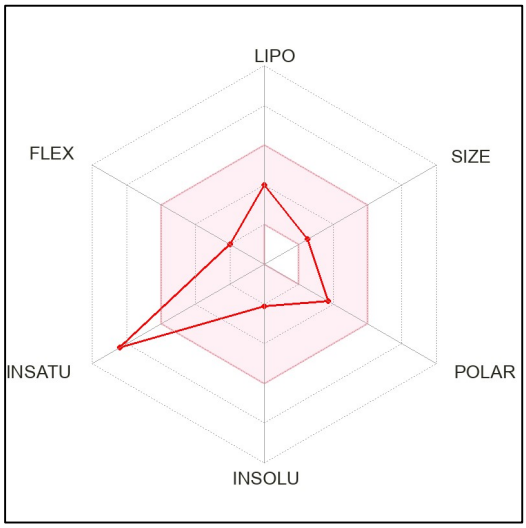
Table 2. Molecular remodelling and bioavailability score

Chemical	Structure	Molecular formula	Bioavailability Score	Lipinski Rule
4-Hydroxybenzoic acid		$C_7H_6O_3$	0.85	Yes
Ferulic acid		$C_{10}H_{10}O_4$	0.85	Yes
p-Coumaric acid		$HOC_6H_4CH=CHCO_2H$	0.85	Yes

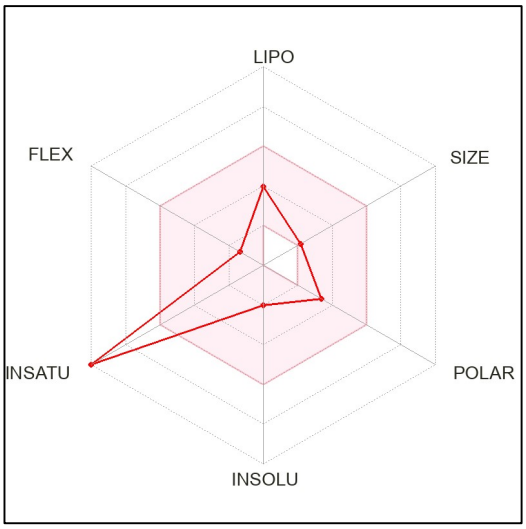
The pharmacophore mapping of the molecules was developed as shown below-



4-Hydroxybenzoic acid



Ferulic acid



p-Coumaric acid

Fig 1. Depiction of pharmacophore mapping

Description of symptoms, gene ID and p-value for different compounds were showed as follows-

Table 3. Description of symptoms, Gene ID and p-value

	scription	alue	ne ID	unt
05417	id and atherosclerosis	6062E-11	S3/SRC/GSK3B/MMP3/JAK2/CDC42/PDPK1/MMP9/CASP1/AKT1/ CASP3/RAC1/AKT2/PPARG/CCL5	
05215	state cancer	3275E-10	K3B/MMP3/PDPK1/FGFR1/GSTP1/MMP9/AKT1/IGF1R/AKT2/RA F1/EGFR	
05205	teoglycans in cancer	7145E-10	C/CDC42/PDPK1/FGFR1/MMP9/TGFB2/AKT1/CASP3/RAC1/ESR1 /IGF1R/AKT2/RAF1/EGFR	
04917	lactin signalling pathway	2507E-09	C/GSK3B/JAK2/STAT1/AKT1/ESR1/AKT2/RAF1/ESR2	

04933	GE-RAGE signalling pathway in diabetic complications	4023E-09	M1/NOS3/JAK2/CDC42/STAT1/TGFB2/AKT1/CASP3/RAC1/AKT2	
05225	patocellular carcinoma	6694E-09	K6/GSK3B/GSTP1/GSTM1/GSTM2/GSTO1/TGFB2/AKT1/IGF1R/AKT2/RAF1/EGFR	
05212	ncreatic cancer	4521E-09	K6/CDC42/STAT1/TGFB2/AKT1/RAC1/AKT2/RAF1/EGFR	
04014	s signalling pathway	0949E-08	C42/FGFR1/RAB5A/AKT1/INSR/RAC1/IGF1R/AKT2/EPHA2/RAF1/EGFR/PAK6/ZAP70	
01522	docrine resistance	5988E-08	C/MMP9/AKT1/ESR1/IGF1R/AKT2/RAF1/ESR2/EGFR	
04151	K-Akt signalling pathway	9944E-08	S3/CDK6/GSK3B/JAK2/PDPK1/FGFR1/AKT1/INSR/RAC1/IGF1R/AKT2/EPHA2/RAF1/EGFR/IL2	

Molecular docking

The compounds were given CID number including 4-Hydroxybenzoic acid (135), Ferulic acid (445858) and p-Coumaric acid (637542). For AKT1 target site, the docking (energy) score was obtained as -5.031kcal/mol, -5.959kcal/mol and -5.193kcal/mol in 135, 445858 and 637542 compounds, respectively. While EGFR target site shown the energy score of -4.390kcal/mol, -4.428kcal/mol and -4.534kcal/mol, respectively. Compound 135 demonstrated the docking score of -3.089kcal/mol, -2.628kcal/mol, -3.476kcal/mol, -2.602kcal/mol, -3.807kcal/mol, -5.115kcal/mol, -4.341kcal/mol and -3.249kcal/mol against target sites- PPARG, STAT1, SRC, MMP9, GSK3B, ESR1, JAK2, and CASP3, respectively. Against target site- ESR1, maximum energy was obtained as -7.062kcal/mol in 445858; -6.395kcal/mol in 637542. In target site- STAT1 the energy score was found lowest as -1.952kcal/mol and -1.365kcal/mol in 445858 and 637542, respectively.

2. Docking score of all the compound against different target sites were shown in below table-

Table 4. Docking score against different target sites

3. Target site	Docking score 135	445858	637542
AKT1	-5.031	-5.959	-5.193
EGFR	-4.390	-4.428	-4.534
PPARG	-3.089	-3.968	-3.986
STAT1	-2.628	-1.952	-1.365
SRC	-3.476	-3.130	-2.556
MMP9	-2.602	-3.575	-2.488
GSK3B	-3.807	-4.311	-3.720
ESR1	-5.115	-7.062	-6.395
JAK2	-4.341	-6.378	-5.769
CASP3	-3.249	-3.848	-2.928

All the compounds were also observed for Parkinson's disease related target sites binding affinity as illustrated below-

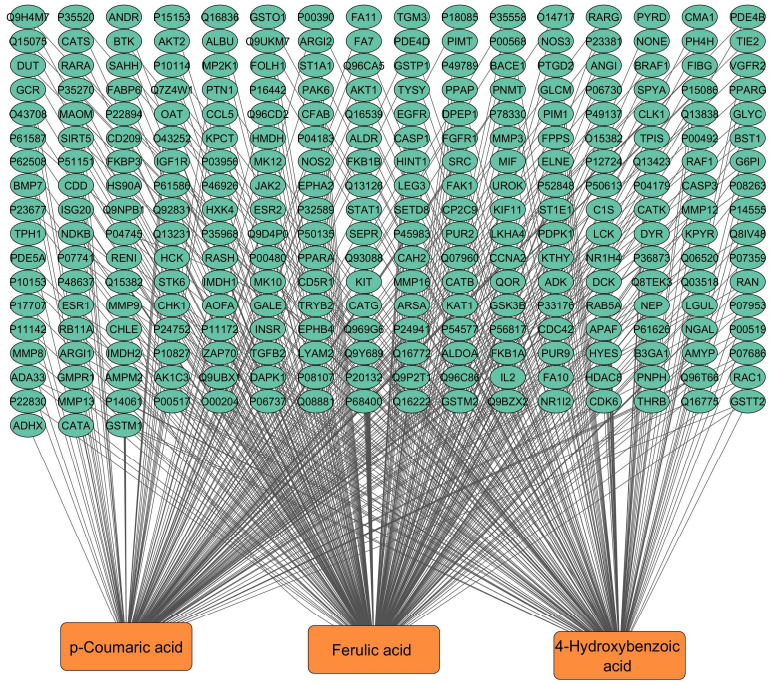
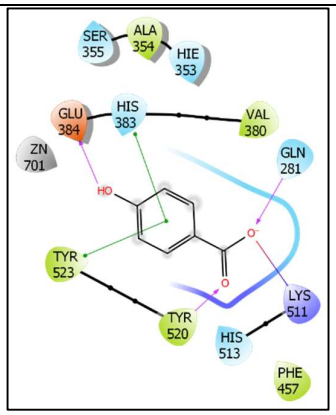


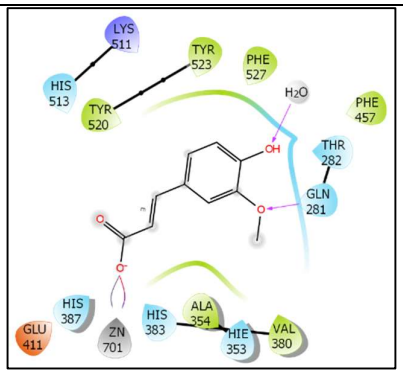
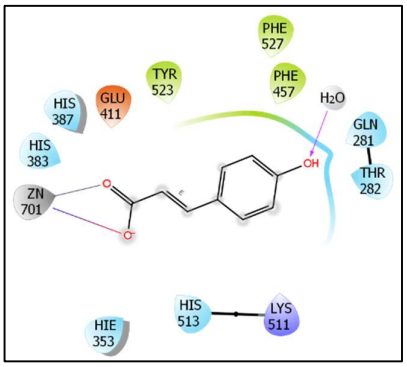
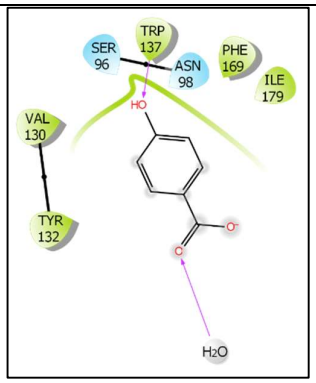
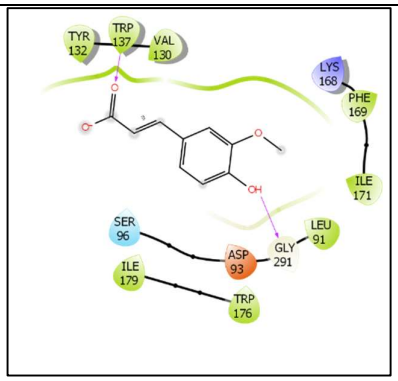
Fig 2. Parkinson's disease related target sites for different compounds

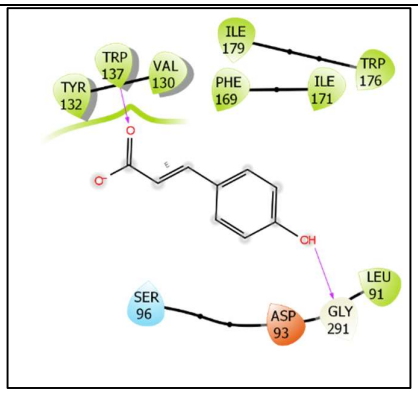
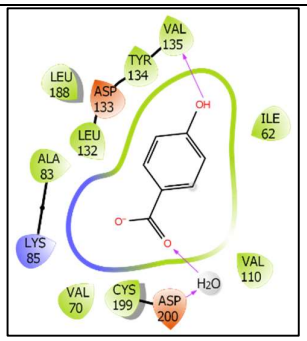
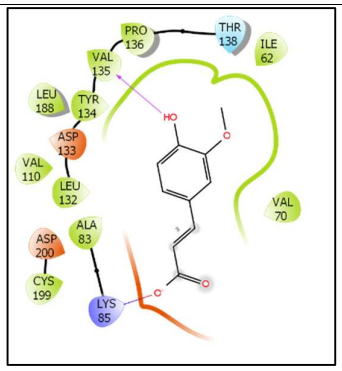
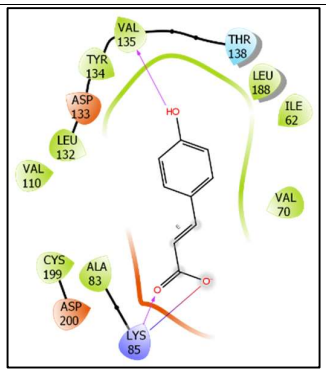
Docking structures

In present study, docking structures were drawn for M1, M2 and M3 against docking 1008, 4DJU, and 1Q5K (PDB ID). Table 5. shows the docking structures for different PBD ID-

Table 5. Docking structures for 1008, 4DJU and 1Q5K (PBD ID)

Compound No.	Docking PDB ID (1008)	
	Docking score	*Docking structure*
M1	-7.215	

M2	-7.199	
M3	-7.064	
Docking PDB ID (4DJU)		
M1	-6.306	
M2	-4.393	

M3	-4.710	
Docking PDB ID (1Q5K)		
M1	-7.080	
M2	-6.445	
M3	-6.426	

For M1, 3 docking structures were drawn with different energy score was observed as -7.215kcal/mol, -

7.199kcal/mol, and -7.064kcal/mol, in PBD ID 1008. M2 compound showed docking scores of -6.306kcal/mol, -4.393kcal/mol, and -4.710kcal/mole, in 4DJU; however, M3 exhibited the energy scores of -7.080kcal/mol, -6.445kcal/mol and -6.426kcal/mol (1Q5K).

For Parkinson's disease, in previous studies, it was found that the three flavonoids (procyanidin, hesperidin, and epicatechin gallate) have higher affinities for the enzyme Aden2A than the PDB ligand (4TG), with respective energy values of −113.727 kcal/mol, −101.446 kcal/mol, and −98.216 kcal/mol.

The flavonoids that exhibited higher score values had residues Asn253, Phe168, Trp246, and Leu249 that showed steric interactions, and hydrogen bonds in hydroxyl groups with residues Asn253, Ala63, His250, and His278, the flavonoids pre-PDB ligand. Key residue interactions for complex formation, including hydroxyl group steric interactions with Lys32, Lys43, and Glu35, were also seen for flavonoid activity. Moreover, these residues were seen in the PDB ligand. The majority of COMT inhibitors, including the most well-known COMT inhibitor medications, tolcapone and entacapone, contain a catechol ring in their structure. The enzymatic COMT demonstrated flavonoid compound activity in our investigations, with epicatechin gallate (−96.205 kcal/mol) exhibiting a more robust interaction than the PDB ligand (BIA = −80.800 kcal/mol). Eight residues, including Asp141, Asn170, Lys144, Met40, and Glu199, exhibited hydrogen connections with the catechol sections of the flavonoids through contacts with the active site for flavonoid activity. Hydrophobic interactions were observed between residues Asn170, Glu199, Trp38, Leu198, Asp141, and Trp143 with the hydroxyl sections of the flavonoids [22].

For anti-Alzheimer's activity, in docking the MAO-B enzyme, two active PDB ligand sites were used. All of the flavonoids in the investigation were shown to be bound to the enzyme at both sites of the active site, exhibiting extremely similar values and the same prevalence of compounds. Additionally, we noticed that subunit B interacts with the chemicals more than subunit A does.

Subunit B values were compared, and we discovered that the following 10 flavonoid interactions were even more active than the PDB binder (4CR = −140 kcal/mol): 3-O-methylquercetin (−140.763 kcal/mol), 8-prenylnaringenin (−145.425 kcal/mol), aspalathin (−150.386 kcal/mol), capensinidin (−140.926 kcal/mol), europinidin (−140.585 kcal/mol), epicatechin gallate (−174.333 kcal/mol), hesperidin (−181.222 kcal/mol), homoeriodictyol (−141.639 kcal/mol), rosinidin (−149.196 kcal/mol), and sterubin (−141.623 kcal/mol). Steric interactions were seen in all of these compounds with the residues Cys172, Tyr435, Leu171, Tyr435, Tyr326, Tyr60, and Gln206. The hydroxyl sections of the flavonoids were shown with hydrogen bonding at Tyr398 and Met436 and Cys397. The human monoamine oxidase (hMAO) isoforms A and B were docked using different flavonoid derivatives (from a Sideritis species) in Turkmenoglu et al.'s study [23].

Result

4-Hydroxybenzoicacid, ferulic acid and p-coumaric acid exhibited the bioavailability score of 0.85 and followed the Lipinski rule. All the compounds were demonstrated almost similar docking score against all the target sites in Parkinson's disease. Among all the PBD ID i.e., 1008, 4DJU, and 1Q5K, maximum energy score was found in PBD ID 1008 that exhibited a significant docking profile of M1, M2 and M3.

Discussion

It suggests that 4-Hydroxybenzoicacid, ferulic acid and p-coumaric acid showed neuroprotective effect that might be effective in the management of Parkinson's disease (PD) and other neurological problems.

FUNDING

Nil.

CONFLICT OF INTEREST

Authors declared for none conflict of interest.

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