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IN-SILICO MOLECULAR DOCKING STUDIES OF FLAVANOIDS AS POTENTIAL ANTI-PARKINSONIAN AGENTS

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Keywords:

Molecular docking, Flavonoids, adenosine A2A receptor, Monoamine oxidase B, Catechol-O-Methyltransferase, Computational chemistry, Molecular visualization, Drug discovery studio

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ABSTRACT: Flavonoids are a class of Polyphenolic compounds found abundantly in plants. This study employs computational methods to predict the binding affinities and interaction patterns of selected flavonoids with the adenosine A_{2A} receptor, Monoamine oxidase B (MAO-B enzyme), and Catechol-O-Methyltransferase (COMT enzymes). The docking simulations were performed using software packages such as iGEMDOCK which utilizes molecular mechanics algorithms to simulate the docking process. Visualization of the docking results was conducted using molecular visualization tools such as Drug Discovery studio (BIOVIA), enabling the analysis of binding modes and interactions between flavonoids and their respective protein targets. This visualization aids in identifying key amino acid residues involved in ligand binding, as well as understanding the structural basis of Ligand-receptor interactions. The findings highlight specific flavonoids that exhibit favourable binding affinities and interactions with the targeted neurochemical receptors and enzymes. Such insights are crucial for guiding further experimental validation and optimization of flavonoid-based compounds as potential therapeutic agents for neurological disorders.

INTRODUCTION: Parkinson's disease is a neurodegenerative disorder that primarily affects movement. It is characterized by symptoms such as tremors, stiffness, slowness of movement, and balance problems. These symptoms result from the progressive loss of dopamine-producing neurons in the brain, particularly in a region called the *Substantia nigra*.

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Flavonoids [1-2] are a group of plant compounds known for their antioxidant [3-4] and anti-inflammatory properties [5-6]. They are commonly found in fruits, vegetables, tea, red wine, and cocoa. In recent years, there has been growing interest in the potential neuroprotective effects of flavonoids, including their role in potentially slowing down the progression of Parkinson's disease [7-8].

Research suggests that flavonoids may exert their neuroprotective effects through various mechanisms, such as reducing oxidative stress, inflammation, and protecting neuronal function. Some specific flavonoids, such as Quercetin, Epicatechin, and Rutin, have shown promising

results in preclinical studies related to Parkinson's disease. However, it's important to note that while these findings are encouraging, much of the research is still in the early stages, and clinical trials are needed to confirm the effectiveness of flavonoids as a treatment for Parkinson's disease in humans.

Targets in Parkinson's disease:

Adenosine A_{2A} Receptors [9-10]: Adenosine A_{2A} receptors are a subtype of G protein-coupled receptors (GPCRs) present on cell surfaces throughout the body, notably in the brain and peripheral nervous system. These receptors play a crucial role in regulating various physiological processes by binding with adenosine, a nucleoside pivotal in energy transfer and neurotransmission. Specifically, adenosine A_{2A} receptors are known for modulating neurotransmitter release, especially dopamine, and influencing neuronal activity within the central nervous system. They are also involved in regulating cardiovascular function and immune responses. In the brain, adenosine A_{2A} receptors are highly expressed in striato pallidal neurons and can form functional complexes with other GPCRs like dopamine D2, metabotropic glutamate mGlu5, and adenosine A1 receptors. Blocking these receptors in striato pallidal neurons reduces the adverse effects of dopamine depletion, thereby alleviating motor impairments associated with Parkinson's disease. Beyond symptom relief, A_{2A} receptor antagonists have shown potential in slowing the progression of Parkinson's by mitigating neurodegeneration and countering the maladaptive neuroplasticity that limits the effectiveness of conventional dopamine replacement therapies.

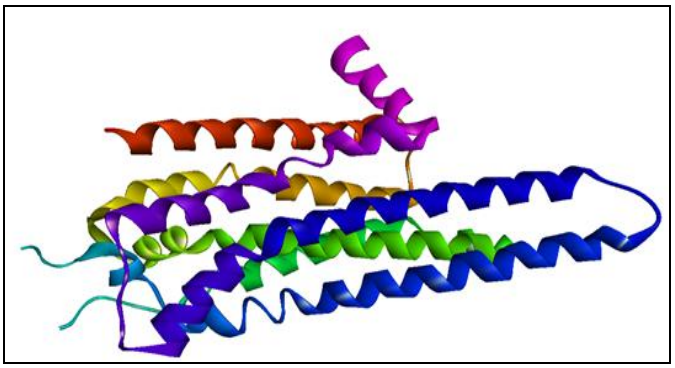


FIG. 1: CLEANED ADENOSINE A_{2A} RECEPTOR PDB ID: 3UZA

Catechol-O-methyltransferase (COMT) [11-12]: Catechol-O-Methyltransferase (COMT) is a crucial enzyme in Parkinson's disease, a progressive neurodegenerative disorder characterized by symptoms such as tremors, stiffness, and slow movement. In Parkinson's, dopaminergic neurons in the substantia nigra, which regulate movement and coordination, gradually degenerate. COMT plays a role in the breakdown of dopamine and other catecholamine's like epinephrine and nor epinephrine. Its activity is vital for regulating dopamine levels in key brain regions such as the prefrontal cortex and striatum, essential for motor function and cognition. The COMT enzyme is structurally characterized by a single domain containing α and β components, organized around a central β sheet with eight helices. Its active site, similar to a Rossmann fold, binds S-adenosyl-L-methionine (AdoMet) and is typical of enzymes interacting with nucleotides. The COMT gene, located on chromosome 22q11, encodes this enzyme crucial for catecholamine degradation, a process impaired in Parkinson's patients. Notably, a polymorphism at codon 158 (Val158Met, designated rs4680) has been identified to reduce COMT enzyme activity, influencing executive cognitive functions. Additionally, this gene locus has implications in schizophrenia, highlighting its broader neurobiological significance.

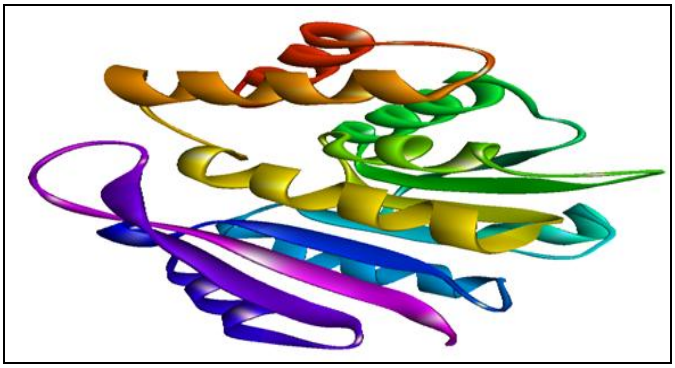


FIG. 2: CLEANED CATECHOL-O-METHYL-TRANSFERASE ENZYME PDB ID: 1H1D

Monoamine oxidase B (MAO-B) [13-14]: Monoamine oxidase B (MAO-B) is a crucial enzyme involved in the metabolism of neurotransmitters like dopamine within the brain. Located on the outer membrane of mitochondria in neurons and glial cells, MAO-B catalyzes the oxidative deamination of dopamine, converting it into metabolites such as 3,4-dihydroxyphenylacetic acid (DOPAC), which are further broken down by other enzymes. This enzymatic activity plays a

pivotal role in regulating levels of dopamine and other monoamines, essential for maintaining neurotransmitter balance and overall brain function. Beyond its fundamental role in neurotransmitter metabolism, MAO-B has garnered significant attention in the context of neurodegenerative diseases, particularly Parkinson's disease. Studies indicate that MAO-B activity is elevated in the brains of individuals with Parkinson's disease, accelerating dopamine breakdown and exacerbating the dopaminergic deficiency characteristic of the disease. Consequently, MAO-B inhibitors such as selegiline and rasagiline have been developed as therapies for Parkinson's disease. These inhibitors work by blocking MAO-B activity, thereby reducing dopamine breakdown and potentially slowing the progression of motor symptoms associated with Parkinson's disease. MAO-B's implications extend beyond Parkinson's disease to encompass other neurological and psychiatric conditions. Its involvement in the metabolism of neurotransmitters like serotonin and nor epinephrine suggests roles in mood regulation and cognitive function. Moreover, MAO-B inhibitors have been explored in contexts beyond neurodegeneration, including depression and Alzheimer's disease, underscoring the enzyme's broader impact on brain health and its potential as a therapeutic target in various disorders.

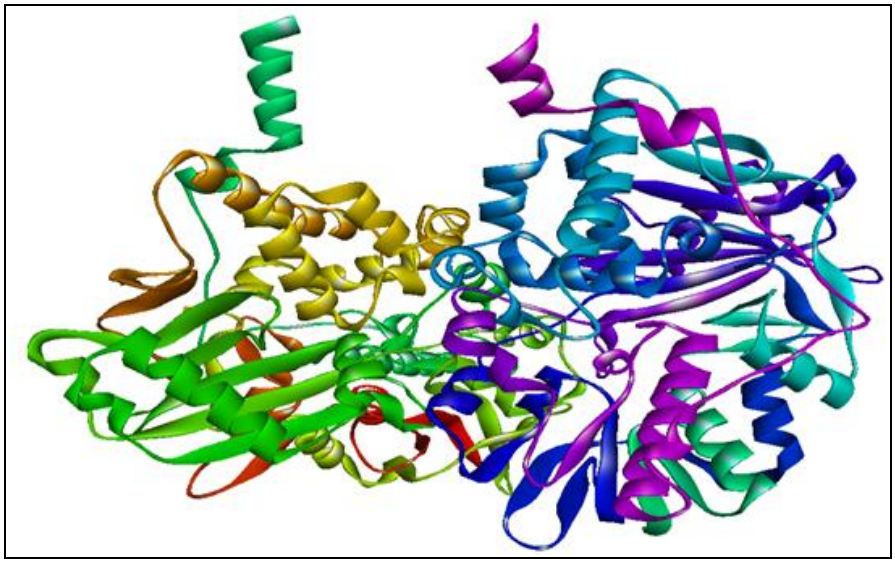
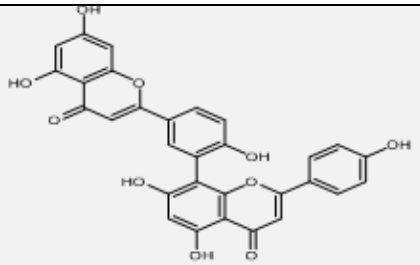
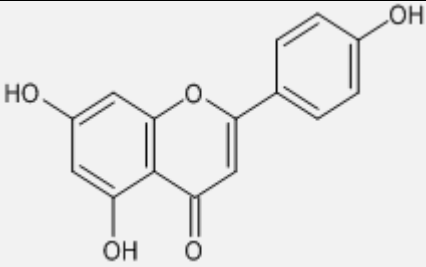
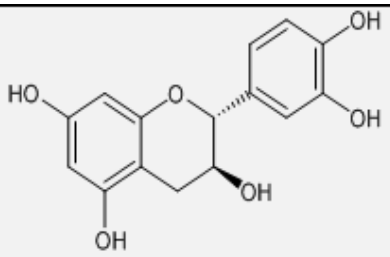
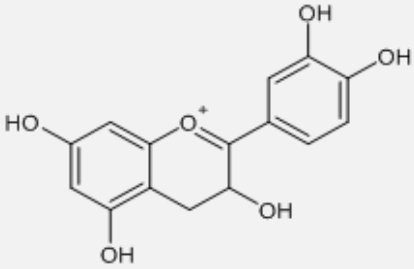
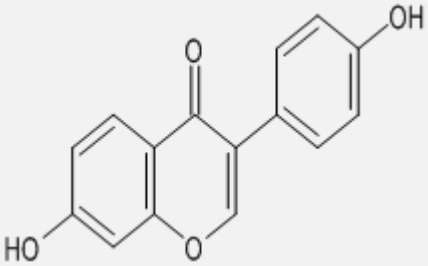
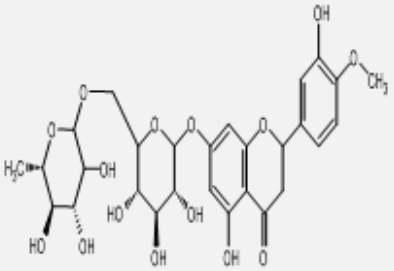
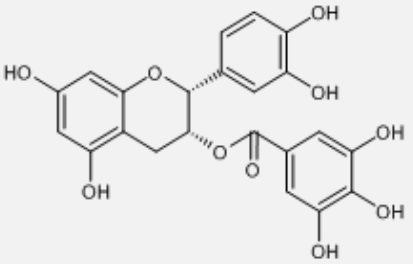
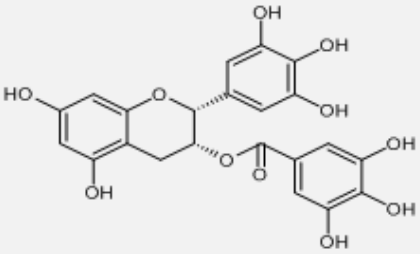


FIG. 3: CLEANED MONOAMINE OXIDASE B (MAO-B) ENZYME PDB ID: 2C65

MATERIALS AND METHODS: To initiate molecular docking studies of flavonoids with the Adenosine A_{2A} receptor, MAO-B enzyme, and COMT enzyme, several preparatory steps are essential. Firstly, the chemical structures of flavonoids are drawn using ChemSketch and saved in formats like mol. These structures are then imported into Avogadro [15-16] for potential optimization through geometry optimization processes. Meanwhile, for the protein structures of adenosine A_{2A} receptor, MAO-B, and COMT, 3D models are obtained from databases such as the Protein Data Bank. Subsequently, Drug Discovery Studio (DDS) [16-17] is employed to pre-process these protein structures, which includes tasks like the removal of water molecules, addition of hydrogen atoms, and assignment of partial charges to ensure the proteins are suitably prepared for docking studies. The actual docking process is facilitated using iGemDock [18-19] where the prepared ligand and protein structures are imported. Docking parameters such as grid size, scoring functions (e.g., binding affinity scoring), and search algorithms (e.g., genetic algorithms) are defined to conduct the docking simulations. These simulations enable the prediction of potential binding modes of flavonoids within the binding sites of the adenosine A_{2A} receptor, MAO-B enzyme, and COMT enzyme. Upon completion of docking simulations, the results are analyzed to interpret the binding poses of flavonoids within each protein's binding site. Docking scores are evaluated to prioritize the most promising flavonoid-protein complexes based on predicted binding affinities. Visual inspection of interactions, facilitated by tools such as iGemDock software and Drug discovery studio, allows for the

examination of molecular interactions such as hydrogen bonding and hydrophobic interactions. The interpretation of results encompasses assessing the significance of docking scores, understanding binding poses, and identifying specific types of interactions observed, such as pi-pi stacking and hydrogen bonding. These steps collectively contribute to elucidating the potential interactions between flavonoids and the studied proteins, offering insights into their therapeutic potential in the context of neurodegenerative diseases like Parkinson's.

TABLE 1: FLAVANOIDS CHOSEN FOR MOLECULAR DOCKING

		
AMENTOFLAVONE	APIGENIN	CATECHIN
		
CYANIDIN	DAIDZEIN	DIOSMIN
		
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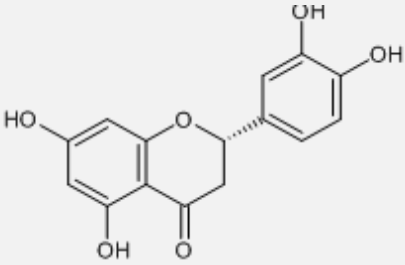	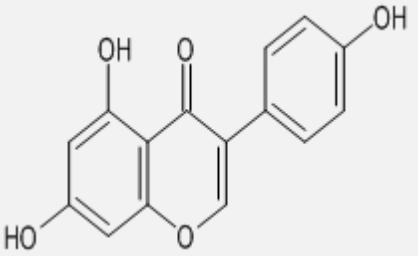	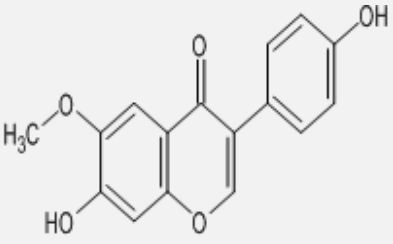
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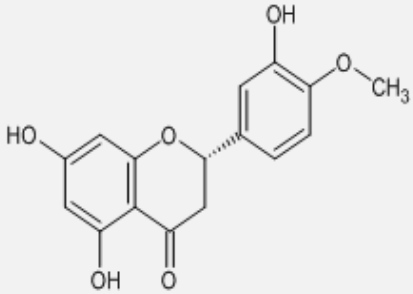	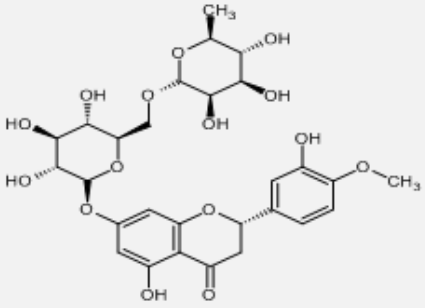	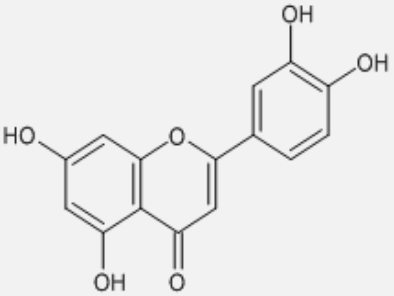

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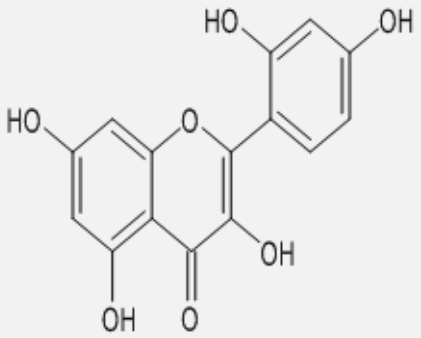
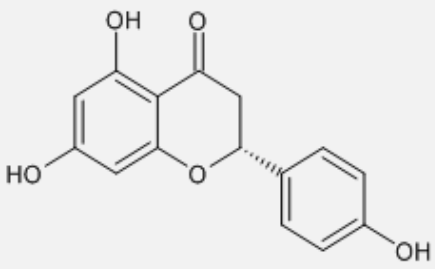
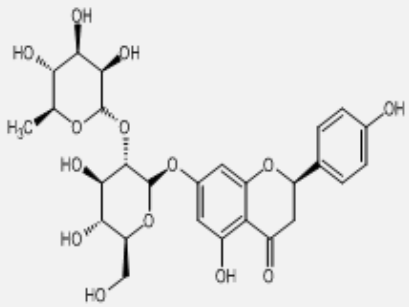


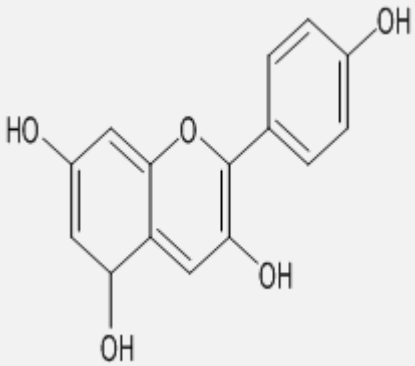
HESPERIDIN



LUTEOLIN



MORIN



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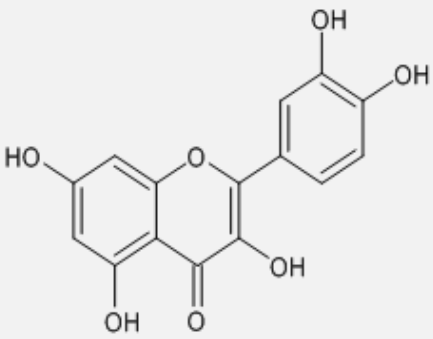

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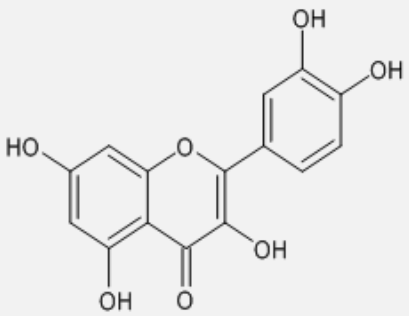
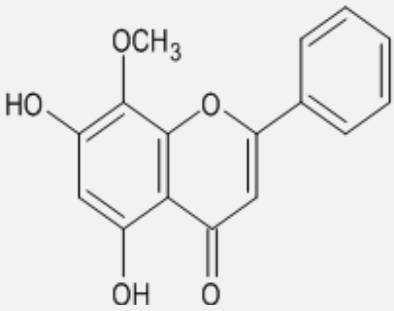


PELARGONIDIN



QUERCETIN

RUTIN

WOGONIN

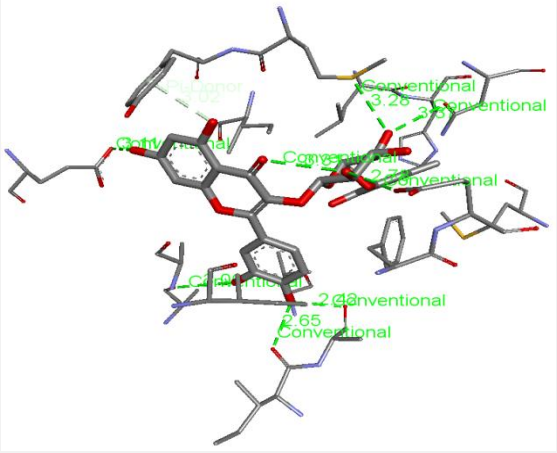
MOLECULAR DOCKING RESULTS:

TABLE 2: MOLECULAR DOCKING DATA OF FLAVONOIDS AND STANDARD COMPOUNDS ON ADENOSINE A_{2A} RECEPTOR

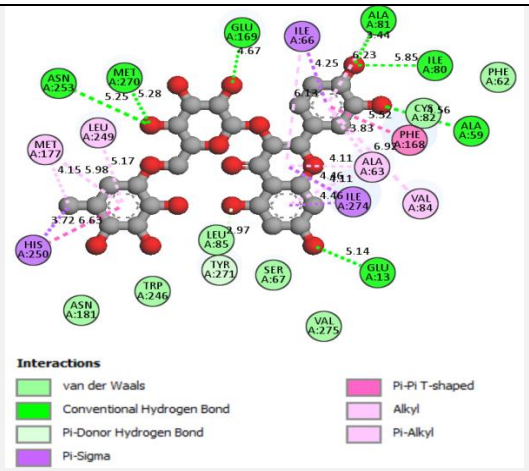
List of Ligands	Total Energy	VDW	H Bond	Elec	Aver Con Pair
Rutin	-128.298	-108.608	-19.6896	0	26.0233
Epigallocatechin 3 gallate	-106.34	-101.394	-4.94607	0	21.5455
Epicatechin 3 gallate	-102.251	-97.4193	-4.83135	0	21.125
Hesperidin	-101.816	-73.4125	-28.404	0	18.4884
Amentoflavone	-100.299	-93.9218	-6.3769	0	16.175
Naringin	-97.5943	-81.8698	-15.7245	0	15.0244
Co-Crystallized Ligand	-92.4672	-76.2461	-16.2211	0	22.1905
Diosmin	-90.5582	-60.4831	-30.0751	0	19.093
Eriodictyol	-89.2355	-71.7265	-17.509	0	25.1429
Epigallacatechin	-88.7985	-65.9998	-22.7987	0	22.8636
Glycitein	-87.227	-73.345	-13.882	0	24.2381
Catechin	-87.0954	-69.0766	-18.0188	0	24.0476
Luteolin	-85.8925	-67.9345	-17.958	0	25.2381
Istradefylline	-85.8342	-76.2525	-9.58176	0	21.4444
Morin	-84.5018	-73.0784	-11.4234	0	23.3636
Hesperetin	-84.2445	-73.1065	-11.138	0	23.0455

Genistein	-83.5359	-70.5408	-12.9951	0	24.75
Quercetin	-83.2893	-71.8872	-11.4021	0	22.0455
Apigenin	-83.1478	-69.2536	-13.8942	0	24.45
Cyanidin	-82.0652	-68.9514	-13.1138	0	26.4762
Daidzein	-81.6566	-70.6846	-10.9721	0	26.4737
Naringenin	-81.5714	-61.6917	-19.8797	0	24.65
Pelargonidin	-81.0371	-79.0677	-1.96948	0	27.15
Wogonin	-78.5983	-70.1492	-8.44914	0	20.381
Caffeine	-57.9644	-53.2006	-4.76374	0	23.3571

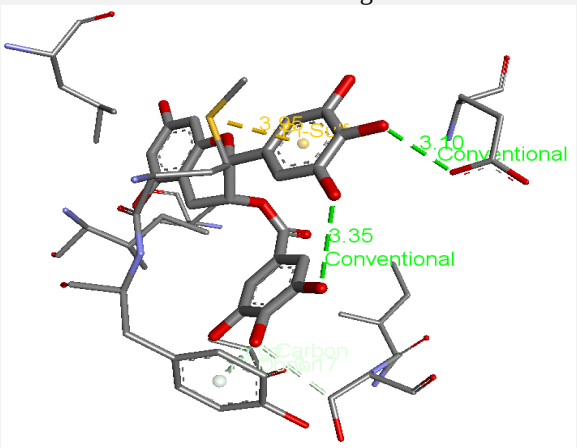
TABLE 3: VISUALIZATION DATA OF FLAVANOIDS AND STANDARD ADENOSINE A_{2A} ANTAGONIST AGAINST ADENOSINE A_{2A} RECEPTOR



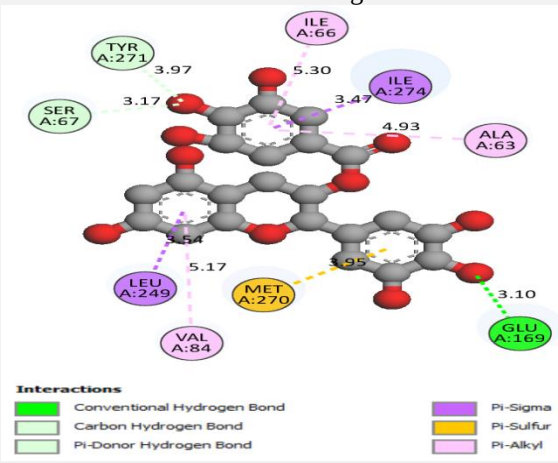
RUTIN 3D image



RUTIN 2D image



EPIGALLAOCATECHIN 3 GALLATE 3D image



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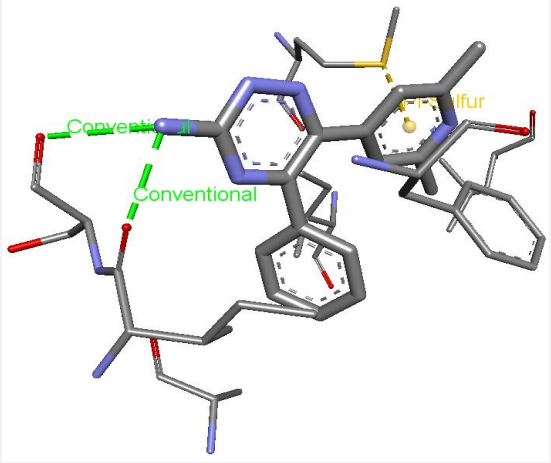
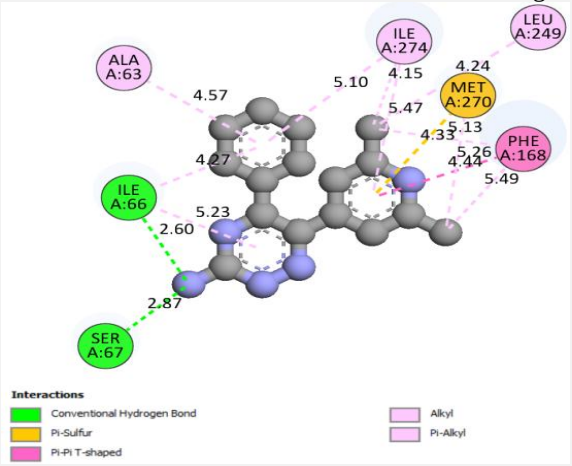


CO-CRYSTALIZED LIGAND 3D image



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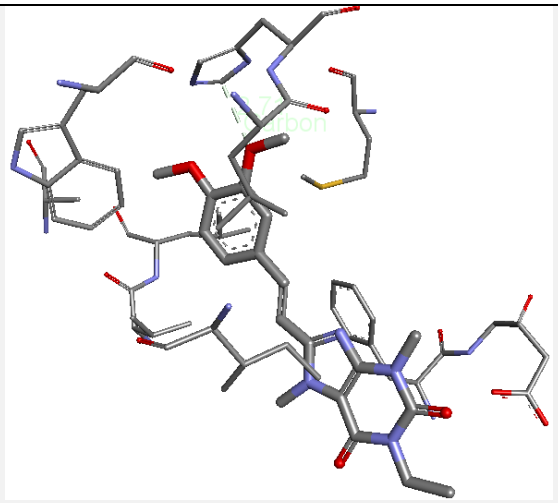

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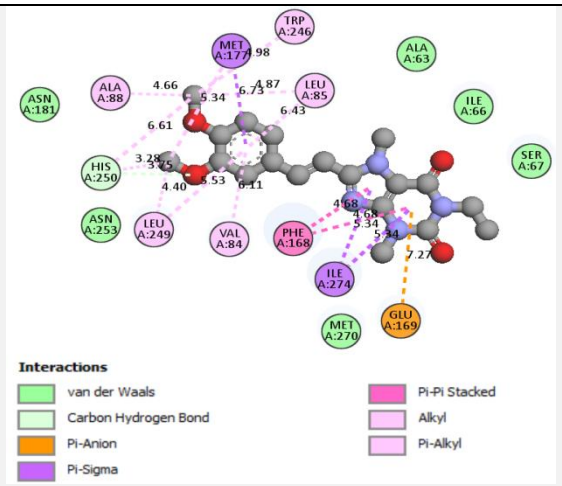

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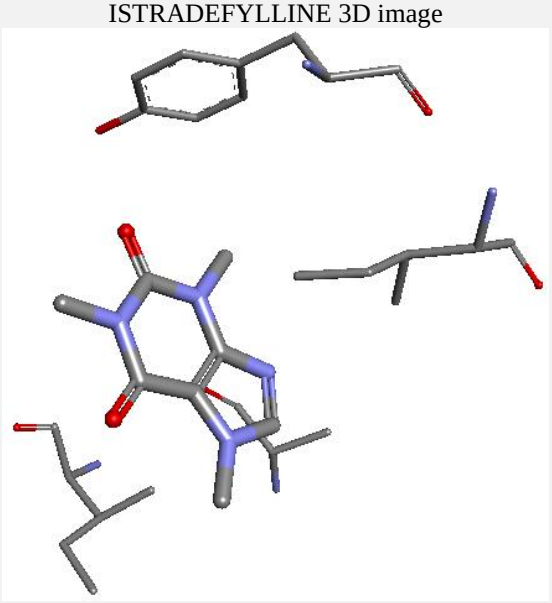
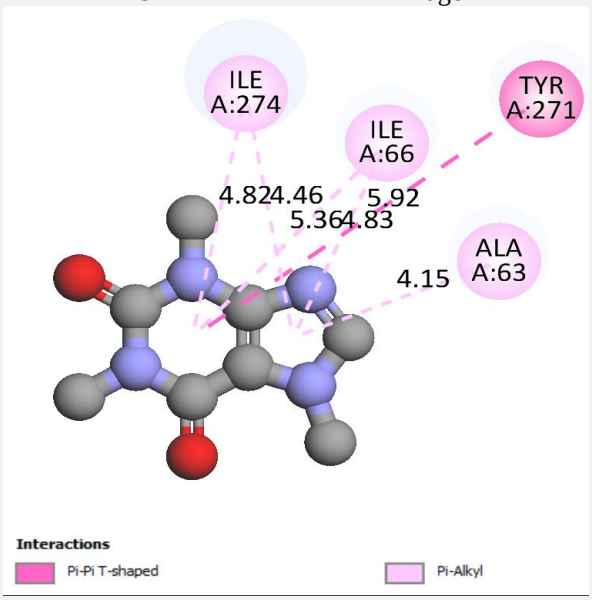


CAFFEINE 3D image



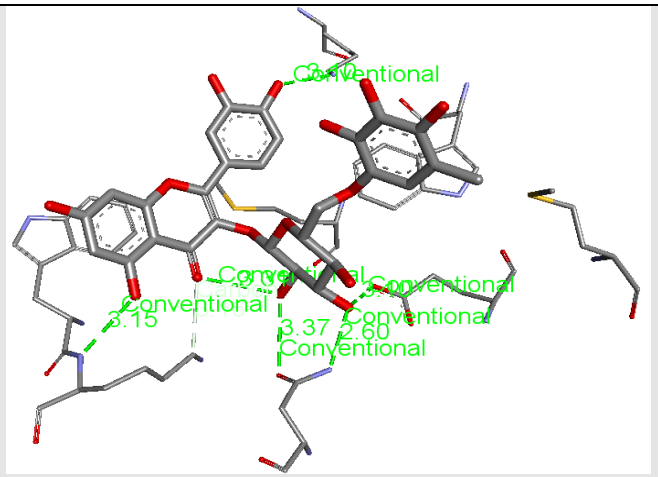
CAFFEINE 2D image

TABLE 4: ENERGY SCORES OF FLAVONOIDS AND STANDARD COMPOUNDS ON COMT ENZYME

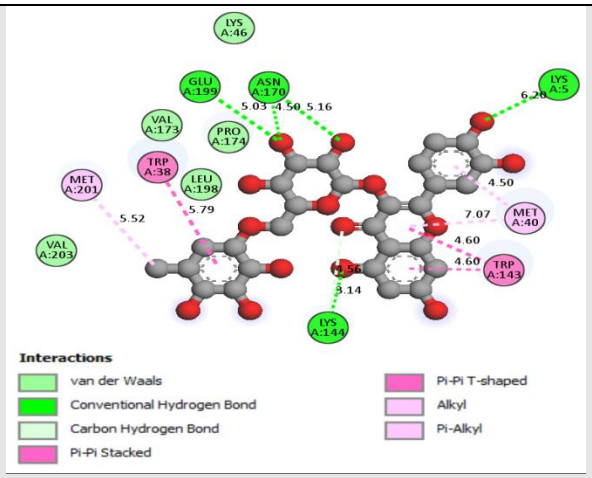
Ligand	Total Energy	VDW	H Bond	Elec	Aver Con Pair
Rutin	-101.49	-84.028	-17.4623	0	14.9302
Co-Crystalized Ligand	-100.71	-80.0766	-21.5851	0.952115	19.1613
Morin	-96.618	-66.0342	-30.5839	0	25.1818
Tolcapone	-93.9686	-65.6767	-29.2181	0.926192	24.7
Hesperidin	-91.9297	-47.2647	-44.665	0	12.907
Diosmin	-89.9918	-66.5668	-23.425	0	15.7674
Epicatechin 3 gallate	-89.3988	-59.9362	-29.4627	0	15
Epigallocatechin 3 gallate	-88.2181	-59.0181	-29.1999	0	14.9091
Quercetin	-86.0765	-66.8565	-19.22	0	20.6364
Naringin	-85.8215	-55.7471	-30.0744	0	12.9512
Wogonin	-84.9996	-65.7796	-19.22	0	23.4762
ENTACAPONE	-84.5441	-60.2809	-25.542	1.27881	21.3636
Amentoflavone	-83.9941	-75.9766	-8.0175	0	14.15
Epigallacatechin	-83.9636	-53.4603	-30.5033	0	17.5
Apigenin	-82.5565	-64.7814	-17.7752	0	24.2
Luteolin	-82.3292	-71.0636	-11.2656	0	24.5714
Catechin	-82.0242	-54.9311	-27.0932	0	22.5238
Cyanidin	-79.4811	-64.9811	-14.5	0	20.0952
Eriodictyol	-79.2455	-69.9658	-9.2797	0	25.6667
Hesperetin	-79.0739	-69.687	-9.38688	0	24.5455

Genistein	-77.8409	-60.3751	-17.4658	0	23.4
Glycitein	-75.5795	-63.4557	-12.1238	0	20.7619
Pelargonidin	-74.6329	-63.7418	-10.891	0	20.65
Daidzein	-72.8578	-53.7163	-19.1415	0	25.5789
Naringenin	-72.5206	-57.4618	-15.0588	0	20.65

TABL 5: VISUALIZATION DATA OF FLAVANOIDS AND STANDARD COMT INHIBITORS AGAINST COMT ENZYME



RUTIN 3D image



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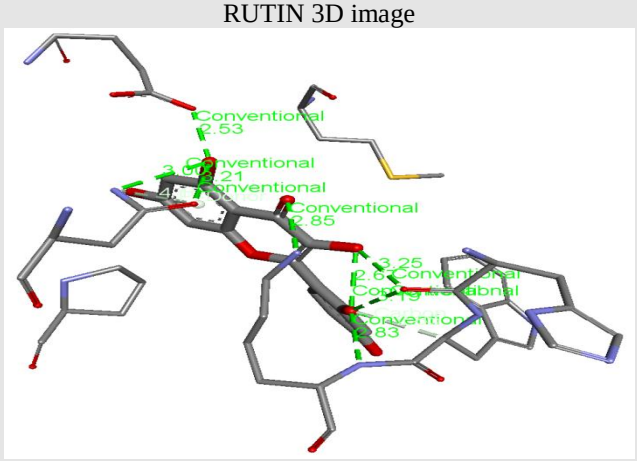
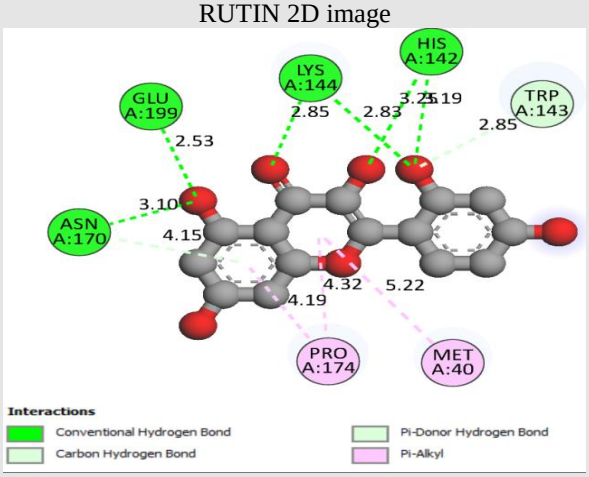


MORIN 3D image



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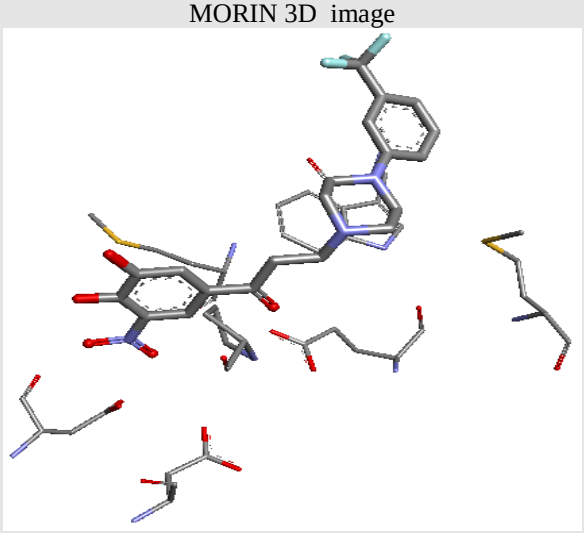
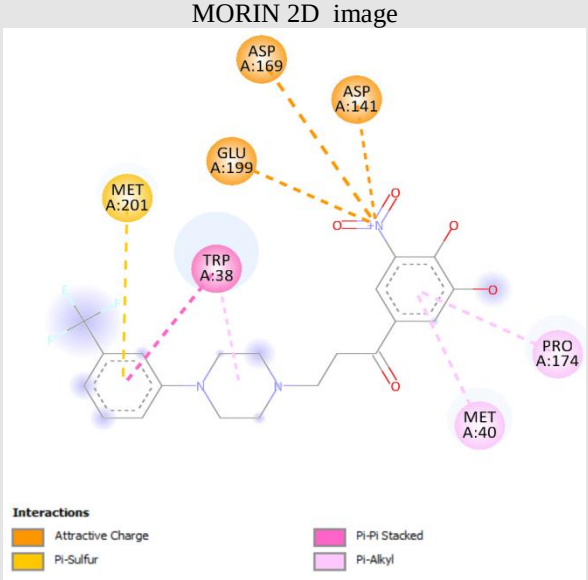


CO-CRYSTALIZED LIGAND 3D image



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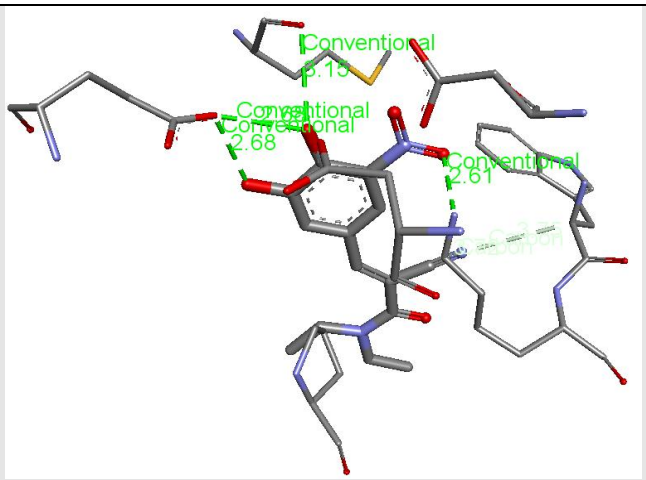
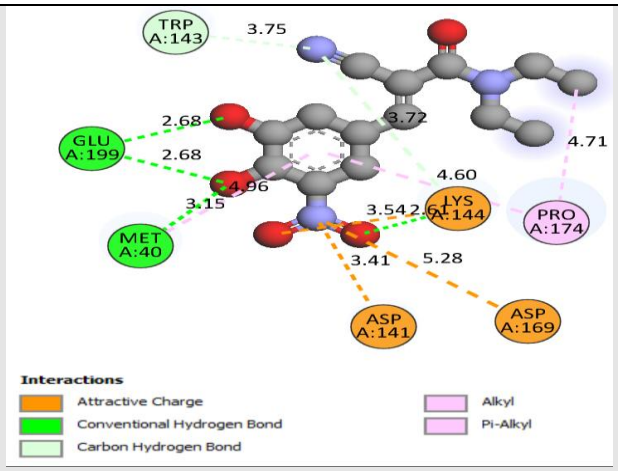


ENTACAPONE 3D image



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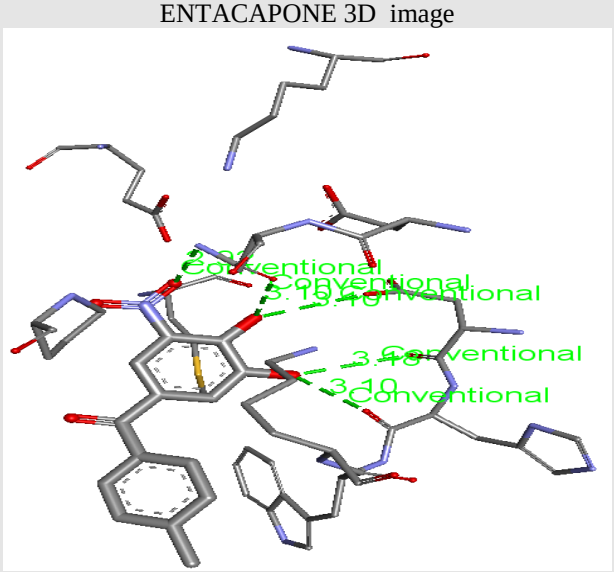
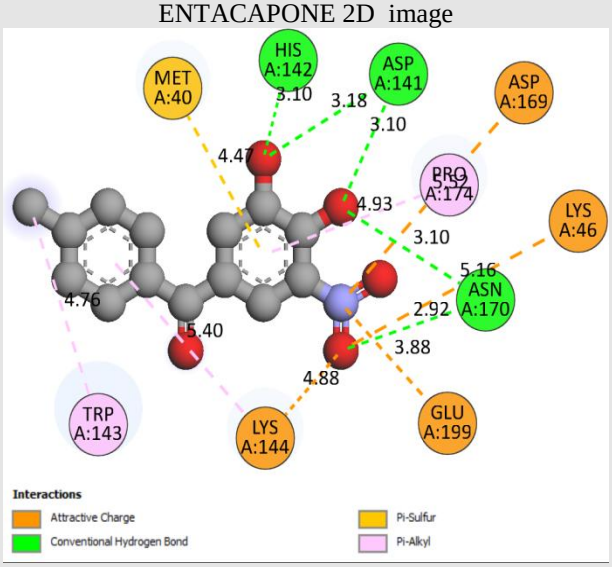


TOLCAPONE 3D image



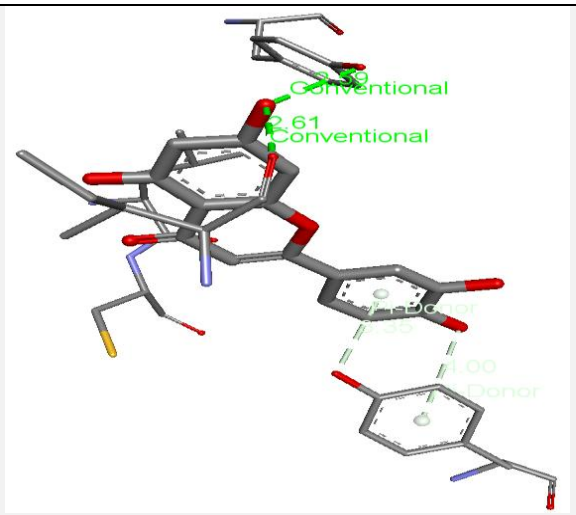
TOLCAPONE 2D image

TABLE 6: ENERGY SCORES OF FLAVONOIDS AND STANDARD COMPOUNDS ON MAO-B TARGET PROTEIN

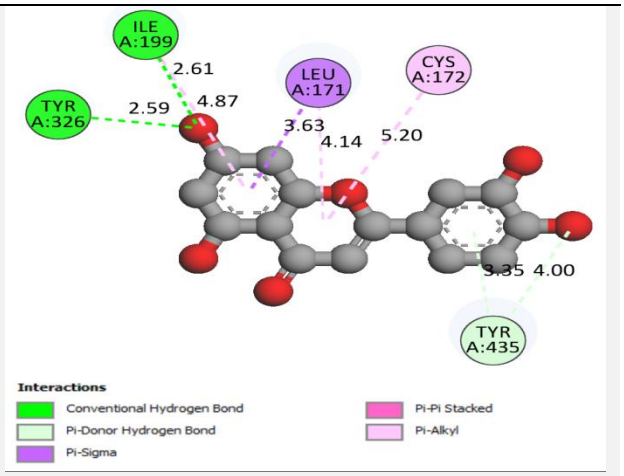
Ligand	Total Energy	VDW	H Bond	Elec	Aver Con Pair
Luteolin	-131.305	-93.1104	-38.1946	0	33.5714
Glycitein	-129.074	-105.256	-23.8184	0	31.5714
Cyanidin	-124.645	-94.0868	-30.5581	0	33.7619
Genistein	-124.066	-102.055	-22.0105	0	34.95
Quercetin	-123.605	-81.951	-41.6542	0	35.0455
Epigallacatechin	-122.6	-101.663	-20.9369	0	36.5
Hesperetin	-122.307	-101.448	-20.8588	0	32.7273
Eriodictyol	-121.541	-105.604	-15.9362	0	35.381
Morin	-119.967	-89.8258	-30.1408	0	35.4091
Daidzein-	-119.026	-97.9422	-21.0835	0	34.8421
Apigenin	-116.238	-99.3285	-16.9097	0	36
Catechin	-113.868	-94.5635	-19.3046	0	32.6667
Wogonin	-112.744	-91.1803	-21.5634	0	33.1905
Pelargonidin	-111.362	-88.9315	-22.4305	0	32.55
Safinamide	-106.525	-106.525	0	0	34.5455
Epicatechin 3 gallate	-93.3255	-71.7557	-21.5698	0	35.25
Naringenin	-92.8681	-68.5431	-24.325	0	32.4
Hesperidin	-92.2417	-66.784	-25.4576	0	12.907
Amentoflavone	-90.6264	-74.1416	-16.4848	0	14.975
Diosmin	-88.4567	-77.7332	-10.7235	0	14.1163
Rutin	-85.5678	-65.9296	-19.6383	0	12.907

Epigallocatechin 3 gallate	-82.1374	-63.3779	-18.7595	0	13.3939
Naringin	-80.3233	-49.9175	-30.4058	0	13.2439
Co-Crystalized Ligand	-79.6938	-79.6938	0	0	32.8571
Rasagiline	-73.7854	-73.7854	0	0	32
Selagiline	-68.4999	-67.6143	-0.8856	0	34.2143

TABLE 7: VISUALIZATION DATA OF FLAVANOIDS AND STANDARD MAO-B INHIBITORS AGAINST MAO-B ENZYME



LUTEOLIN 3D image



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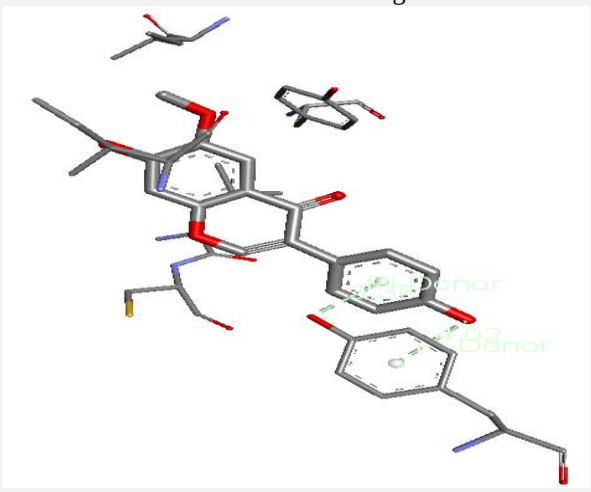

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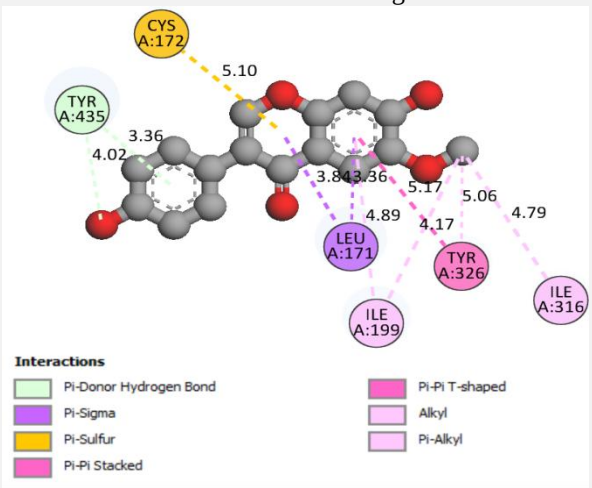

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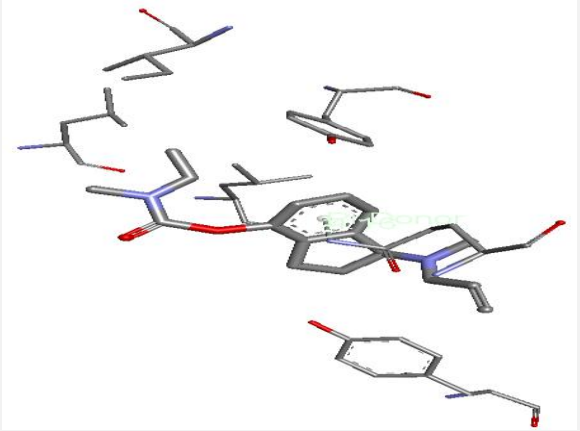
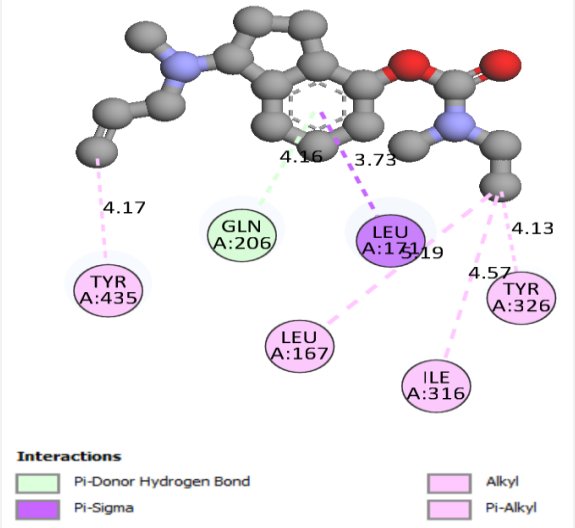
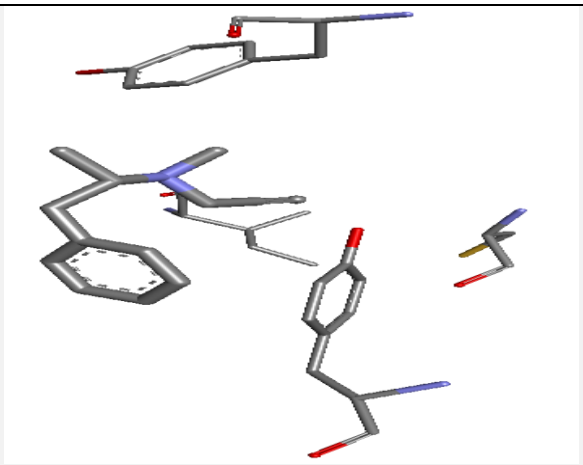


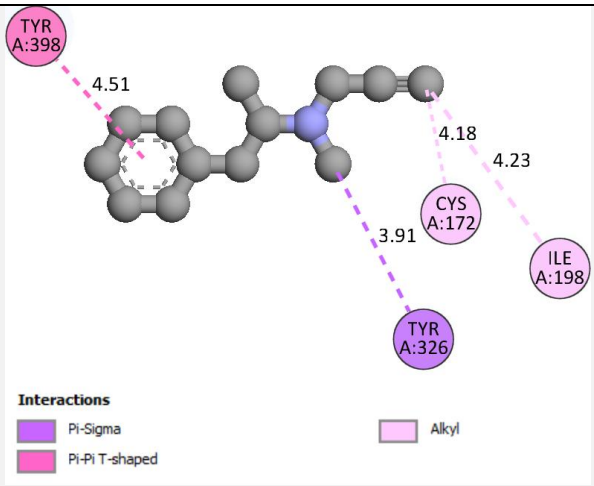
CO-CRYSTALIZED LIGAND 3D image



CO-CRYSTALIZED LIGAND 2D image



SELAGILINE 3D image



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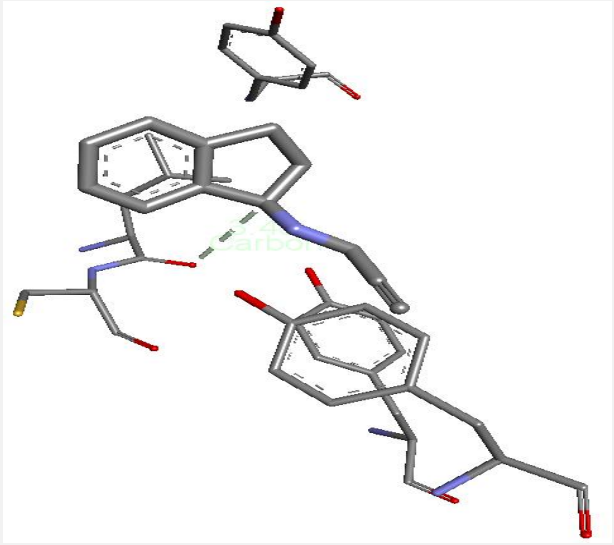
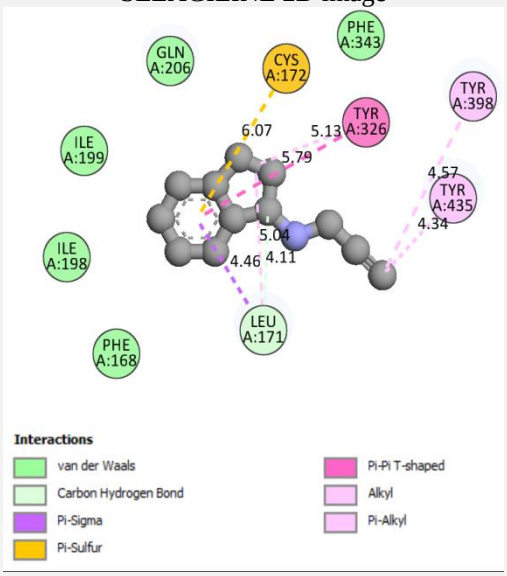


RASAGELINE 3D image



RASAGELINE 2D image

RESULTS AND DISCUSSION:

Target Adenosine A_{2A}: Based on molecular docking studies targeting the Adenosine A_{2A} receptor, Rutin [20-21] and Epigallocatechin-3-gallate [22-23] emerge as highly promising ligands with notable binding affinities of -128.29 kcal/mol and -106.34 kcal/mol, respectively.

Rutin demonstrates the strongest interaction, and forms seven conventional hydrogen bonds with Adenosine A_{2A}receptor ASN: 253, MET: 270, GLU: 169, ALA: 81, ILE: 80, ALA: 59, GLU: 13 indicating it are potential as a robust candidate for therapeutic development targeting this receptor. Epigallocatechin-3-gallate also exhibits substantial binding affinity and forms one conventional hydrogen bond with adenosine A_{2A} receptor GLU: 169 suggesting it could be explored further as a viable compound for drug development. Standard Adenosine A_{2A} receptor antagonist Istradefylline [24-25] and caffeine [26-27] will not forms conventional hydrogen bonds. Both natural compounds outperform the standard ligands Istradefylline (-85.83 kcal/mol) and caffeine (-57.96 kcal/mol), underscoring their potential advantages in terms of receptor binding strength. The co-crystallized ligand, with a binding affinity of -92.46 kcal/mol, serves as a reference point, confirming that Rutin and Epigallocatechin-3-gallate surpass this benchmark. These findings highlight Rutin and Epigallocatechin-3-gallate as promising leads warranting further experimental validation, including *in-vitro* and *in-vivo* studies, to substantiate their potential therapeutic efficacy targeting the adenosine A_{2A} receptor.

Target COMT Enzyme: In the molecular docking study targeting the catechol-O-methyltransferase (COMT) enzyme, Rutin and Morin emerged as top ligands with promising binding affinities of -101.49

kcal/mol and -96.61 kcal/mol, respectively. These natural compounds demonstrate strong interactions with the COMT enzyme, suggesting their potential as effective inhibitors or modulators of COMT activity. Comparatively, the standard COMT inhibitors Entacapone (-84.54 kcal/mol) and Tolcapone (-93.96 kcal/mol) showed lower binding affinities than Rutin and Morin, indicating that these natural flavonoids may offer competitive advantages in terms of binding strength. The co-crystalized ligand, with a binding affinity of -100.71 kcal/mol, provides a reference point confirming the favorable binding energies of Rutin and Morin. Rutin forms four conventional hydrogen bonds with COMT enzyme GLU: 199, ASN: 170, LYS: 144, LYS: 5 and Morin forms Four conventional hydrogen bonds ASN:170, GLU: 199, LYS: 144, HIS: 142. And standard COMT inhibitors [28-29] Entacapone forms two conventional hydrogen bonds GLU: 199, MET:40 and Tolcapone forms three hydrogen bonds HIS:142, ASP:141, ASN: 170. These results underscore Rutin and Morin as promising candidates for further investigation in drug development targeting COMT, potentially offering novel therapeutic approaches for disorders influenced by COMT enzyme activity. Future studies including biochemical assays and *in-vivo* experiments are essential to validate and expand upon these computational findings.

Target MAO-B Enzyme: In the molecular docking study aimed at targeting the monoamine oxidase-B (MAO-B) enzyme, Luteolin and Glycitein emerged as top ligands with remarkably high binding affinities of -131.30 kcal/mol and -129.07 kcal/mol, respectively. These findings highlight Luteolin and Glycitein as potent inhibitors of MAO-B activity, potentially offering robust therapeutic potential in conditions where MAO-B inhibition is beneficial. Leuteolin forms two conventional hydrogen bonds with MAO-B enzyme TYR: 326, ILE: 199 and Glycitein were not form hydrogen bond. Compared to the standard MAO-B inhibitors [30-31] rasagiline -73.78 kcal/moland selegiline -68.49 kcal/mol, Luteolin and Glycitein exhibit significantly stronger binding interactions, suggesting they may provide enhanced efficacy in enzyme modulation. The co-crystalized ligand, with a binding affinity of -79.69 kcal/mol, serves as a benchmark confirming the superior binding energies of Luteolin and Glycitein. These results underscore the potential of Luteolin and Glycitein as lead compounds for further exploration in drug development targeting MAO-B enzyme, warranting subsequent experimental validation through biochemical assays and preclinical studies to substantiate their therapeutic promise.

CONCLUSION: The present study on molecular docking reveal that Rutin, Epigallocatechin-3-gallate, Morin, Luteolin, and Glycitein are promising natural compounds with high binding affinities for their respective targets. Rutin and Epigallocatechin-3-gallate outperform standard antagonists at the Adenosine A2A receptor, while Rutin and Morin show superior binding to the COMT enzyme compared to traditional inhibitors. Luteolin and Glycitein exhibit strong interactions with MAO-B, surpassing standard inhibitors in binding affinity. These findings highlight the potential of these natural compounds as leads for drug development, warranting further experimental validation to confirm their therapeutic efficacy.

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CONFLICTS OF INTERESTS: Authors declare no conflicts of interest.

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