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Research Article

In Silico Evaluation of Molecular Interactions for Parkinson's Disease Drug Discovery

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Abstract:

Monoamine oxidase B (MAO-B) and Catechol-O-methyltransferase (COMT) inhibitors are crucial for the treatment of Parkinson's disease (PD). Inhibition of these enzymes involves both natural and synthetic compounds. Passiflora incarnata serves as a significant source of natural bioactive molecules, primarily flavonoids (including Apigenin, Luteolin, Myricetin, Orientin, Quercetin, Kaempferol, Vitexin, Isovitexin, and Isoorientin) and alkaloids (such as Harman, Harmine, Harmol, Harmaline, Harmalol, 8-hydroxy Harmine, and Harmine N-oxide). Synthetic options include inhibitors such as Rasagiline, Selegiline, and Safinamide (targeting MAO-B), as well as Entacapone, Tolcapone, and Opicapone (targeting COMT).
In this study, molecular docking was employed to identify ligands with optimal interaction energies for each enzyme and to characterize binding affinities, thereby aiding the potential design of new inhibitors. The docking analysis of natural compounds revealed that flavonoids exhibited the strongest affinities and consistent interaction patterns; notably, Myricetin demonstrated the most effective binding to both MAO-B and COMT. Among the synthetic compounds, Safinamide displayed the highest affinity for MAO-B, while Opicapone showed the highest affinity for COMT. These findings highlight the potential of both natural and synthetic inhibitors in reducing enzyme activity associated with PD, providing valuable insights for the development of more effective therapeutic agents.

1. Introduction

The treatment of neurodegenerative diseases constitutes one of the most critical challenges in modern medicine. In terms of frequency, morbidity, and complexity, Parkinson's disease (PD) represents a paramount pathology involving the degeneration of the nervous system.PD is the second most prevalent neurodegenerative disease. This pathology is characterized by the progressive loss of dopaminergic neurons of the pars compacta in the substantia nigra[1,2]. The irreversible loss of 70–80% of these neurons leads to the appearance of the main symptoms of the disease: resting tremor, muscle rigidity, bradykinesia, and postural instability[3].Dopamine bioavailability in the central

nervous system is closely associated with the activity of two enzymes: monoamine oxidase-B (MAO-B) and catechol-O-methyltransferase (COMT), both of which are involved in the dopamine inactivation pathway[4-6]. While MAO-A inhibitors are typically used in anti-depressive therapy, MAO-B inhibitors are established in Parkinson's therapy. Currently, the MAO-B inhibitors selegiline, rasagiline, and safinamide have been approved for the treatment of Parkinson's disease. Clinical studies were initiated in the 1970s[7,8], originating from the concepts of Riederer and Youdim[9]. Selegiline was introduced in the 1980s, followed internationally by rasagiline 20 years later. Finally, safinamide was approved in numerous countries and launched on the market as of 2015.Catechol-O-methyltransferase (COMT) is the primary enzyme responsible for inactivating the catechol neurotransmitter dopamine and the drug L-dopa[10]. L-dopa is utilized in the clinical treatment of central nervous system (CNS) disorders such as Parkinson's disease[11] and potentially others, including schizophrenia[12,13] and depression[14]. Its efficacy is directly linked to the level of dopamine converted from the drug. Studies have shown that inhibition of COMT activity results in a marked reduction of the body clearance of L-dopa and dopamine[15], leading to sustained dopamine levels in the brain and improved therapeutic efficacy[16,17]. The critical role of COMT in the treatment of Parkinson's disease has promoted research aimed at designing potent and selective COMT inhibitors. Several such inhibitors are currently used as adjuncts to L-dopa therapy. Available COMT inhibitors include tolcapone, entacapone, and the more recently approved opicapone[18]. These inhibitors possess structures based on pharmacophores derived from nitrocatechol, a characteristic that may lead to certain adverse effects[19-22].

Plant extracts and their constituents represent significant natural sources of antioxidants. The antioxidant activity observed in many plant extracts is primarily attributed to secondary metabolites, particularly phenolic compounds such as flavonoids, alkaloids, and tannins. The potent antioxidant capacity of flavonoids is regarded as one of their most relevant biological properties, underpinning many of their physiological effects in the body[23]. Indeed, numerous studies have reported the neuroprotective effects of flavonoids[24-26]. In addition, our previous studies have demonstrated the potential of natural and synthetic compounds as enzyme inhibitors using molecular docking and theoretical approaches[27,28,29]. Passiflora incarnata L. (*Passifloraceae*), commonly known as maypop or passionflower, is a medicinal plant with a long history of global use as an anxiolytic and sedative[30]. Native to the tropical regions of the Americas, its aerial parts have traditionally been employed, notably in the United States, for the treatment of anxiety, nervousness, and neuralgia[31]. This traditional use aligns with pharmacological literature, which frequently describes flavonoids from Passiflora species as antioxidant and neuroprotective agents.

The leaves of P. incarnata are characterized by a flavonoid content of approximately 0.25%, including vitexin, isovitexin, orientin, isoorientin, apigenin, and kaempferol. Beyond flavonoids, the plant contains various indole alkaloids based on a β-carboline ring system, such as harman, harmine, harmalol, and harmaline. Other identified phytoconstituents include carbohydrates, essential oils, amino acids, and the cyanogenic glycoside gynocardin[32]. Consequently, the administration of P. incarnata to individuals with chronic insomnia may offer therapeutic benefits for sleep disorders, memory impairment, and degenerative brain diseases. Specifically, Passiflora preparations may aid in the treatment of insomnia through sedative properties that facilitate sleep onset[33]. Thus, flavonoids and related constituents from Passiflora species are consistently recognized as antioxidant and neuroactive compounds in pharmacological studies.

The present study was designed to evaluate the inhibitory potential of natural and synthetic compounds against monoamine oxidase-B (MAO-B) and catechol-O-methyltransferase (COMT), two key enzymes implicated in Parkinson's disease. The natural inhibitors investigated are derived from *Passiflora incarnata* and consist primarily of flavonoids and alkaloids, while the synthetic series includes established drugs such as rasagiline, selegiline, and safinamide (for MAO-B), as well as entacapone, tolcapone, and opicapone (for COMT). Molecular docking was employed to characterize the formation of enzyme–inhibitor complexes. This in silico approach allows for the detailed analysis of interaction patterns between the ligands (both natural and synthetic) and their respective enzymatic targets, providing insights into mechanisms that may delay disease progression.

2. Materials and Methods

2.1 Preparation of enzymes

The PDB structures used, i.e. MAO-B (6RKP) , COMT (6I3C), were obtained from the RCSB Protein Data Bank (www.rcsb.org).[32]

In Figure 1, each enzyme active site together with its co-crystallised ligand is shown.

2.2 Preparation of ligands.

The structures obtained were optimized at the density functional theory (DFT) level using the hybrid functional B3LYP (Becke three-parameter exchange; Lee–Yang–Parr correlation) with the 6-31G* basis set in Gaussian 05[35]. According to recent studies, the natural (flavonoid and alkaloid) and synthetic inhibitors considered for each enzyme in this work were identified, and their molecular structures together with their physicochemical properties are presented in Tables 1,2. Lipinski's rule of five,[36] a valuable tool for selecting suitable candidates by predicting drug-like properties, was also evaluated for all ligands. Geometry optimization was performed using the MMFF94x force field,[37] as implemented in MOE, and the semiempirical Hamiltonian AM1[38.] The docking results were subsequently refined using the force-field energy. This computational protocol is consistent with methodologies reported in our previous DFT-based studies [39,41].

2.3 Docking and Building Complexes

The next step consists of positioning the ligands in the enzyme active site. For this, we used the Molecular Docking Module in the MOE software. Once the ligand-receptor complex is formed, the most stable conformation is adopted and will show the lowest energy.

3. Results and Discussion

The molecular docking results and interactions for the two best natural inhibitors and the best synthetic inhibitor are presented in Tables 3 and 4 and, Figures 2 and 3. The ligand interactions were visualized using an improved 2D depiction layout algorithm, with protein residues arranged around the ligand to indicate spatial proximity. Residues are labeled with their three-letter amino acid code and sequence number[42,43]. In systems containing multiple chains, positions are prefixed by the corresponding letter. Interactions between 2.5 Å and 3.1 Å are considered strong, while those between 3.1 Å and 3.55 Å are moderate. Interactions greater than 3.55 Å are considered weak[44].

3.1 Synthetic Compounds

These results indicate that Safinamide exhibits the lowest binding energy (-8.4074 kcal/mol), suggesting it is the most effective synthetic inhibitor capable of forming the most stable complex.As shown in Figure 2, the Safinamide–enzyme complex features two key interactions: a hydrogen bond donor interaction with Glu206 (Chain A) and a pi–H interaction with Ile199 (Chain A). These interactions occur at distances of 3.44 Å and 4.48 Å, with interaction energies of -2.3 kcal/mol (moderate interaction) and -0.8 kcal/mol (weak interaction), respectively.

3.2 Interaction to Catechol-O-methyltransferase

Natural Compounds

These results indicate that Myricetin, a flavonoid, exhibited the lowest binding energy (-6.4672 kcal/mol). This suggests it is the most effective natural inhibitor tested and forms the most stable complex.

The complex (Fig. 3) formed by Myricetin, identified as the most potent natural inhibitor exhibiting the highest stability with catechol-O-methyltransferase (COMT), interacts with several key amino acid residues. Specifically, it engages with Glu90 (A) via a hydrogen bond donor, Asp141 (A) through two distinct ionic interactions, and Met40 (A) via a pi–H interaction. These interactions occur at distances of 3.25, 3.22, 3.66, and 4.05 Å, respectively. The first two contacts (Glu90 and the first Asp141 interaction) represent moderate interactions, while the latter two (second Asp141 interaction and Met40) are considered weak.

The interaction energies range between -7.2 and -0.8 kcal/mol. Additionally, the presence of six residues, Gln120, Ser119, Gly66, Ser72, Tyr71, and Val42, contributes to the stability of the complex, likely through electrostatic or hydrophobic forces. These findings suggest that Myricetin possesses significant binding affinity for COMT, effectively interfering with the active site residues Glu90, Asp141, and Met40.[25]

3.3 Synthetic Compounds

These results indicate that Opicapone exhibits the lowest binding energy (-6.5183 kcal/mol), identifying it as the most effective synthetic inhibitor capable of forming the most stable complex.

The complex formed by Opicapone with catechol-O-methyltransferase (Fig. 3) involves multiple interactions with key amino acid residues. Specifically, Opicapone interacts with Cys95 (A) and Glu199 (A) via hydrogen bond donors, and forms extensive ionic interactions with Asp141 (A) and Glu199 (A), as well as a pi–H interaction with Met 40 (A). The interaction distances are 3.94, 2.52, 3.87, 2.60, 3.58, 3.86, 3.86, 2.52, and 3.98 Å, respectively. Among these, the interactions at 2.52

Å and 2.60 Å are classified as strong, while the others are considered weak.

The interaction energies range from -8.6 to -0.8 kcal/mol. Furthermore, the presence of residues Leu286, Phe329, and Trp82 contributes additional stability, likely through hydrophobic or electrostatic forces. These findings confirm that Opicapone possesses significant binding affinity for catechol-O-methyltransferase, effectively interfering with the active site residues Cys95, Glu199, Asp141, and Met40[45].

The graphical legend for the 2D interactions is shown in Fig. 4

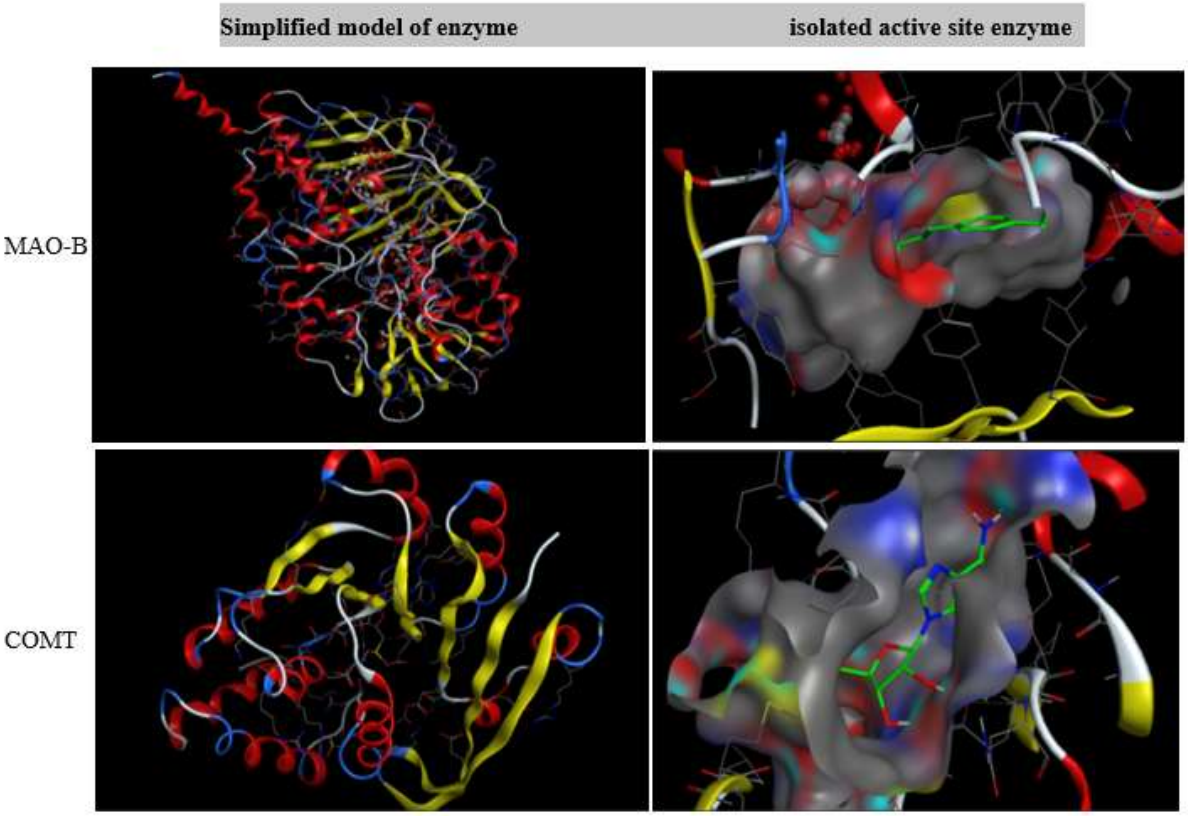
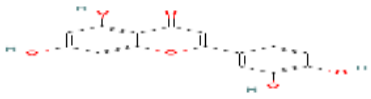
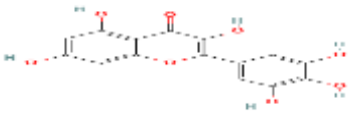
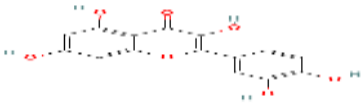
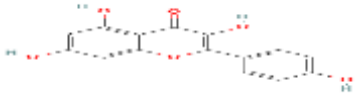
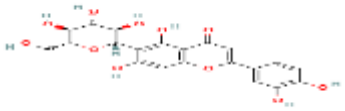


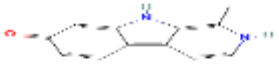
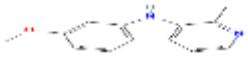
Figure 1 *Simplified models and isolated active sites of the MAO-B and COMT enzymes*

Table 1 *Natural (flavonoid and alkaloid) and synthetic inhibitors evaluated for MAO-B and COMT*

Ligand	IUPAC name	Structure	PubChem CID
Flavonoids inhibitors			
Apigenin	5,7-dihydroxy-2-(4-hydroxyphenyl)chromen-4-on		5280443
Luteolin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromen-4 one		5280445
Myricetin	3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)chromen-4-one		5281672
Quercetin	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one		5280343

Orientin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one		5281675
Kaempferol	3,5,7-trihydroxy-2-(4-hydroxyphenyl)chromen-4-one		5280863
Isovitexin	5,7-dihydroxy-2-(4-hydroxyphenyl)-6-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one		162350
Vitexin	5,7-dihydroxy-2-(4-hydroxyphenyl)-8-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one		5280441
Isoorientin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one		11477

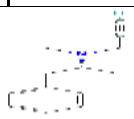
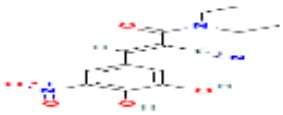
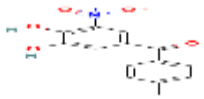
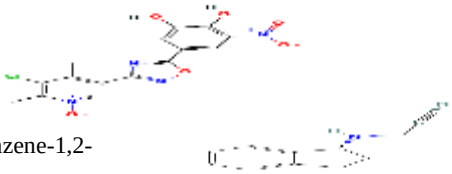
Alkaloids inhibitors

Harman	1-methyl-9H-pyrido[3,4-b]indole		5281404
Harmol	1-methyl-2,9-dihydropyrido[3,4-b]indol-7-one		68094
Harmine	7-methoxy-1-methyl-9H-pyrido[3,4-b]indole		5280953
Harmaline	7-methoxy-1-methyl-4,9-dihydro-3H-pyrido[3,4-b]indole		3564
Harmalol	1-methyl-4,9-dihydro-3H-pyrido[3,4-b]indol-7-ol1-methyl-4,9-dihydro-3H-pyrido[3,4-b]indol-7-ol		3565
Harmin N-oxide	2-hydroxy-7-methoxy-1-methylpyrido[3,4-b]indole		85853001
8-hydroxy harmine	7-methoxy-1-methyl-9H-pyrido[3,4-b]indol-8-ol		129845702
Harmaline-on	7-methoxy-4,9-dihydro-3H-pyrido[3,4-b]indole-1-		137209017

	carbaldehyde		

Synthetic polyphenols inhibitors of MAO-B

Table 2 *Physicochemical properties of natural and synthetic inhibitors targeting MAO-B and COMT*

Rasagiline	1-methyl-2,9-dihydropyrido[3,4-b]indol-7-one		3052776
Selegiline	(2R)-N-methyl-1-phenyl-N-prop-2-yn amine;hydrochloride		26758
Safinamide	(2S)-2-[[4-[(3-fluorop phenyl]methylamino]propanamide		131682
	Synthetic polyphenols inhibitorso of COMT		
Entacapone	-2-cyano-3-(3,4 nitrophenyl)-N,N enan		5281081
Tolcapone	(3,4-dihydroxy-5-n (4-meth		4659569
Opicapone	5-[3-(2,5-dichloro-4, oxidopyridin-1-ium oxadiazol-5-yl]-3-nitrobenzene-1,2-		

Ligand	Weight	TPSA	Log P	Log S	H-bonds donors	H-bonds acceptors	Toxicity
Physicochemical properties of flavonoids							
Apigenin	270.24	87 10 7 14 8	2.42	-3.46	3	5	No
Luteolin	286.24	12	2.13	-3.10	4	6	No
Myricetin	218.23	7	1.72	-2.41	6	8	No
Quercetin	302.23	19	2.01	-2.71	5	7	No
Orientin	448.4	7	-0.26	-2.56	8	11	No
Kaempférol	286.24	10	2.31	-3.14	4	6	No
Isovitexin	432.4	7	2.71	-3.82	2	4	No
Vitexin	432.4	66.	0.03	-2.92	7	10	No
Isoorientin	448.4	8 17 7 19 7	-0.26	-2.56	8	11	No
Physicochemical properties of alkaloids							
Harman	182.22	28.7	3.02	-2.58	1	1	Yes
Harmol	198.22	41.1	1.26	-2.42	2	3	No
Harmine	212.25	37.9	3.03	-2.63	1	2	Yes
Harmaline	214.26	37.4	2.54	-2.47	1	2	No
Harmalol	200.24	48.4	2.24	-2.06	2	2	No
Harmine N-oxide	228.25	37.3	2.29	-2.57	1	3	Yes
8-hydroxy harmine	228.25	58.1	2.74	-2.27	2	3	Yes
Rasagiline	171.24	12	1.99	2.18	1	1	No
Selegiline	223.74	3.2	-2.43	-2.56	1	1	No
Safinamide	302.34	64.4	2.90	-3.84	2	4	No

Synthetic Inhibitors of MAO-B

Table 3 *Binding energies of complexes formed between natural and synthetic ligands with MAO-B and COMT (kcal/mol)*

Compound	Enzyme ; energy (kcal/mol)		
	MAO-B	**COMT**	
Native ligand	-8.2764	-8.7594	
Flavonoids			
Apigenin	-6.9535	-5.9239	
luteolin	-6.8949	-6.3851	
Myricetin	-7.4501	-6.4672	
Quercetin	-7.4066	-6.3734	
Orientin	-5.4522	-5.9223	
Kaempferol	-7.1629	-6.1692	
Isovitexin	-7.1140	-5.1802	
Vitexin	-6.6236	-5.3769	
Isoorientin	-6.8579	-6.4662	
Alkaloids			

Harman	-5.8336	-4.9425	
Harmol	-5.7687	-4.9526	
Harmin	-6.0949	-5.0235	
Harmalol	-5.7329	-4.2748	
Harmine-N-oxide	-5.9583	-5.6531	
8-hydroxy harmin Harmalin-on	-6.2517 -6.3205	-5.1281 -5.7298	

Synthetic Inhibitors of MAO-B			
Rasagiline	-5.9473	-	
Selegiline	-6.3152	-	
Safinamide	-8.4074	-	

Synthetic Inhibitors of MAO-B

Entacapone	-	-6.0550
Tolcapone	-	-5.9932
Opicapone	-	-6.5183

Table 4 *Interaction patterns of natural and synthetic ligands with MAO-B and COMT amino acid residues*

Interactions of the best natural ligands with MAO-B amino acid residues					
Compound	**Ligand**	**Receptor**	**Interaction**	**Distance (Å)**	**E (kcal/mol)**
Myricetin	O7 7	SG CYS 172	(A) H-donor	3.60	-1.8
Interactions of the best natural ligands with COMT amino acid residues					
Myricetin	N 1	OE2 GLU 64	(A)Ionic	3.95	-0.6
	N 1	OD2 ASP 141	(A)Ionic	2.40	-10.0
	O2 2	OE1 GLU 90	(A)H-donor	3.25	-1.0
	O3 3	OD1 ASP 141	(A) Ionic	3.22	-3.2
Interactions of the best synthetic ligand with MAO-B amino acid residues					
Safinamide	N4 4 6-ring	OE1 GLN 206 CB ILE 199	(A) H-donor (A) pi-H	3.44 4.48	-2.3 -0.8
Interactions of the best synthetic ligand with COMT amino acid residues					
Opicapone	CL1 1	SG CYS 95	(A) H-donor	3.94	-2.0
	O5 5	OE2 GLU	(A) H-donor	2.52	-1.2
	O5 5	199	(A) ionic	3.87	-0.8
	O6 6	OD1 ASP	(A) ionic	2.60	-7.8
	O6 6	141	(A) ionic	3.58	-1.6
	O6 6	OD2 ASP	(A) ionic	3.86	-0.8
	O6 6	141	(A) ionic	3.86	-0.8

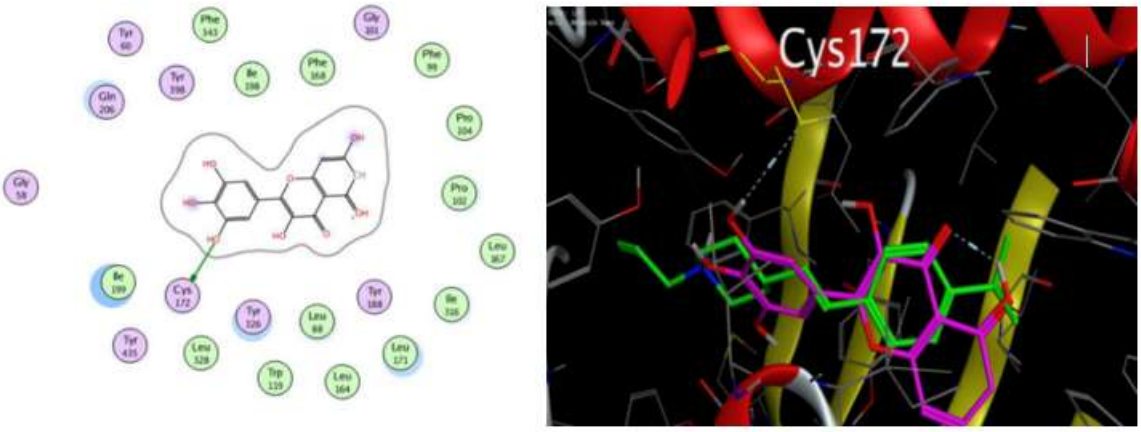
	O6 6 6-ring	OD1 ASP 141 OD2 ASP 141 OE1 GLU 199 OE2 GLU 199 CB MET 40	(A) ionic (A) pi-H	2.52 3.98	-8.6 -0.9

Interaction to Monoamine oxidase

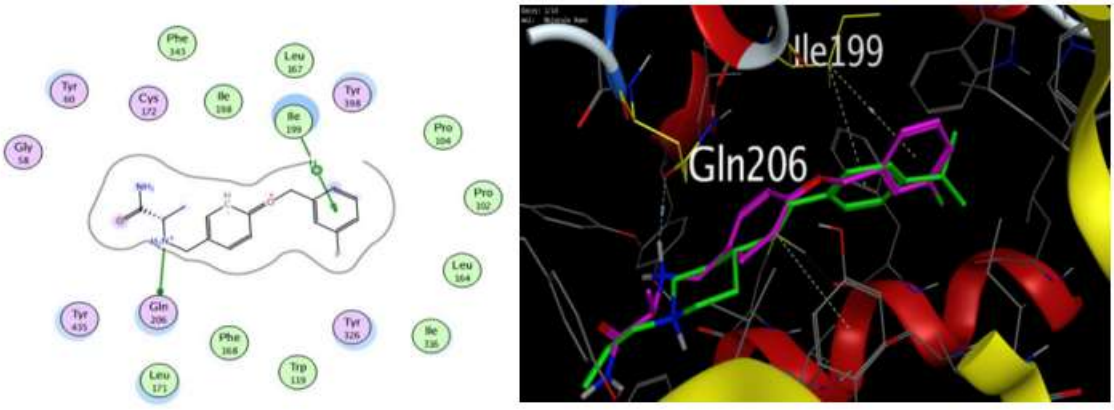
Natural Compounds

These results show that Myricetin, a flavonoid, exhibited the lowest binding energy (-7.4501 kcal/mol). This suggests it is likely the most effective natural inhibitor among those tested, forming the most stable complex.

The complex (Fig. 2) formed by Myricetin, the most potent natural inhibitor exhibiting the highest stability with monoamine oxidase-B (MAO-B), interacts with the amino acid residue Cys172 (Chain A) via a hydrogen bond donor. This interaction occurs at a distance of 3.60 Å, indicating a weak interaction, with an interaction energy of -1.8 kcal/mol.



(MAO-B - Myricetin) complex



(MAO-B - Safinamide) complex

Figure 2 *Interaction diagrams (MAO-B - ligand)*

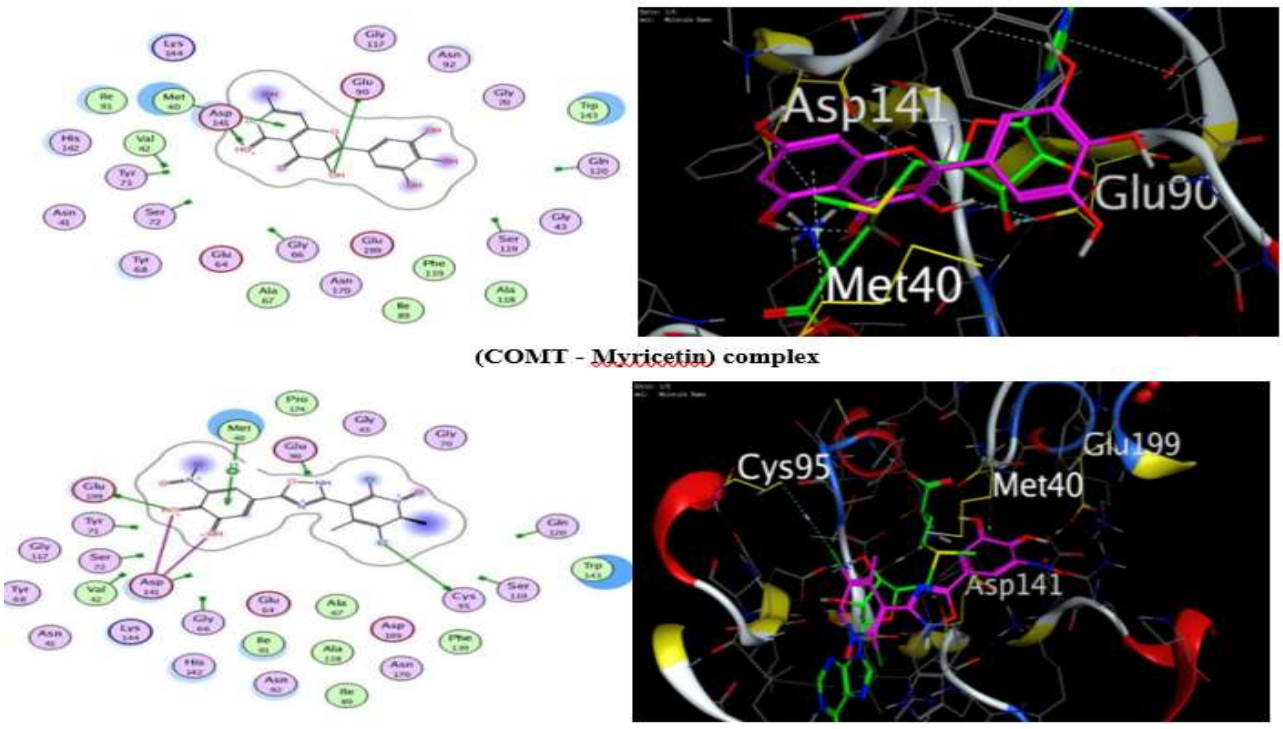


Figure 3 — *Interaction diagrams (COMT - ligand)*

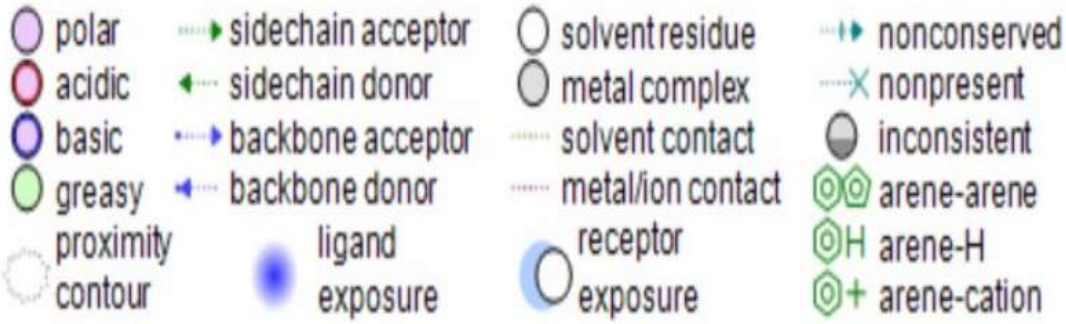


Figure 4 — 2D graphical legend

4. Conclusions

The work presented in this study primarily utilizes molecular docking to calculate key parameters, such as docking scores and binding energies, to better elucidate the inhibition mechanisms relevant to Parkinson's disease (PD). The results reveal that flavonoids exhibit the highest affinity for the target enzymes, characterized by the lowest binding energy values and consistent interaction models. Specifically, the natural compound Myricetin, alongside the synthetic agents Safinamide and Opicapone, emerged as the most promising candidates to potentially retard the progression of this pathology.

Notably, the natural compounds investigated comply with Lipinski's rules for oral drug administration.46,47 A comparison of these inhibitors suggests that natural compounds could play a significant role in the effective treatment of PD. Given their favorable safety profile and lack of reported side effects, these molecules warrant further in-depth study to validate their activity and inhibitory potency in broader cohorts. These findings are highly significant for the fields of phytotherapy and the prevention of neurodegenerative diseases

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- **Ethical approval:** The conducted research is not related to either human or animal use.
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