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Multitargeted Molecular Docking and ADMET Profiling of Potent Bioactive Compounds from *Atropa acuminata* for Parkinson's disease Treatment

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Abstract

Atropa acuminata plant has excellent potential for the treatment of several brain disorders. Phytochemical compounds in this plant act as antioxidants, preserving synaptic plasticity and preventing neuronal degeneration. The neurodegenerative condition Parkinson's disease has emerged as one of the most significant health concerns of the twenty-first century. A detailed in silico molecular docking study was carried out to assess the neuroprotective effects of *Atropa acuminata* compounds against three potential targets of PD, including monoamine oxidase B (MAO-B), adenosine A2A receptor (AA_2AR), and dopamine D2 receptor (D2R). Physicochemical and pharmacokinetic properties were also investigated. In this docking study, the *Atropa acuminata* compounds Belladonnine and Apoatropin showed a superior docking score with target proteins of -9.5 kcal/mol and -9.1 kcal/mol for MAO-B, -8 kcal/mol and -6.7 kcal/mol for AA_2AR, and -8.5 kcal/mol and -6.7 kcal/mol for D2R. On the basis of the reference drug, they showed good docking scores. Furthermore, it is crucial to carry out in vitro and in vivo investigations to enhance the potency of *Atropa acuminata* components and understand the processes underlying the suppression of Parkinson's disease-related enzymes.

Introduction

In the Kashmir Himalayas, medicinal plants like *Atropa acuminata, Saussurea costus,* and *Podophyllum hexandrum* are essential to traditional and modern medical procedures. These medicinal plants are essential to folk, Ayurvedic, and Unani medicine, and current studies are still investigating their pharmacology. They have been utilized for ages in traditional medical procedures and are prized for their possible health benefits. Due to the factors of growing interest in natural bioactive compounds, worries about the side effects of synthetic and semi-synthetic compounds, and a desire for sustainable healthcare solutions, the use of phytochemical compounds of medicinal plants is becoming more popular worldwide [1].*A.acuminata* is a medicinal plant that belongs to the Solanaceae family, and in the Kashmir Himalayan region this medicinal plant is critically endangered. This herb attracts interest because of its possible therapeutic importance and socioeconomic

relevance, and it is recognized for its pharmacological significance and commercial value [2].

Parkinson's disease (PD), which affects 2–3% of those 65 years of age and above, is the second most common neurodegenerative disease [3]. A progressive loss of dopaminergic neurons in regions of the brain like the substantia nigra, decreased dopamine levels, and the formation of Lewy bodies, which are deposits of alpha-synuclein protein, are the hallmarks of Parkinson's disease [3-6]. Evidence suggests that oxidative stress (OS), which is linked to other pathological pathways such as alpha-synuclein proteostasis, mitochondrial dysfunction, calcium dyshomeostasis, axonal transport dysfunction, and neuroinflammation, is crucial to the onset and development of Parkinson's disease (PD), even though the exact cause of the disease is still unknown. A feedback loop that speeds up neurodegeneration is created when these factors interact to increase oxidative stress [3,7]. Crucially, existing PD drugs only manage the symptoms, such as motor and non-motor symptoms, highlighting the need for effective treatments that are able to modify disease progression.

Treatment approaches mainly concentrate on increasing dopaminergic levels and finding non-dopaminergic drugs. The non-dopaminergic drugs include anticholinergics and glutamate antagonists. These therapeutic interventions include drugs that target the dopaminergic system, such as Levodopa, dopamine agonists, Monoamine Oxidase-B (MAO-B) inhibitors, and Catechol-O-methyltransferase (COMT) inhibitors to delay the physical and psychological symptoms [8]. In order to develop molecules that can act on numerous targets in neurodegenerative illnesses like Parkinson's disease (PD), the Multi-Target Directed Ligands (MTDLs) strategy is becoming increasingly important in neurochemistry [9]

For neurodegenerative diseases, traditional drug design, which concentrates on a single target per medication, is not effective[10].Reliance on a single medication that targets a single protein makes it more likely that resistance may emerge as a result of mutations in active target areas. Researchers are now concentrating on small molecule-based MTDLs, which have little affinity for other cellular proteins but can affect several pharmacologically important targets within the Central Nervous System (CNS) [11].These MTDLs have favourable toxicological and physicochemical characteristics that lessen the possibility of negative effects. Furthermore, MTDLs

exhibit a unified pharmacokinetic and pharmacodynamic profile and may have synergistic or additive effects [12].

Table 1: Phytochemical compounds reported in *A.acuminata*

Sr. No	Compound Name	Compound ID	Molecular Formula
1	Hyoscyamine	64692	C17H23NO3
2	Tropinone	446337	C8H13NO
3	Hyoscine N Oxide	3000667	C17H21NO5
4	Atropine Oxide	3000668	C17H23NO4
5	Cuscohygrine	1201543	C13H24N2O
6	Coumarin	323	C9H6O2
7	Tropan	637986	C8H15N
8	Nicotine	89594	C10H14N2
9	Acetosyringone	17198	C10H12O4
10	Acetovanilione	2214	C9H10O3
11	Acetophenone	7410	C8H8O
12	Belladonnine	442995	C34H42N2O4
13	Apoatropin	64695	C17H21NO2
14	Methyl Vanillate	19844	C9H10O4

Materials and Methods

Screening for Phytochemical compounds in *Atropa acuminata*

Through the database IMPPAT (Indian plants, phytochemistry and Therapeutics) and Pubchem [13, 14].We search for *A.acuminata* to obtain the phytochemical compounds Shown in Table 1.

Retrieval of Targets Protein

For the present study, Crystal structure of human MAO-B(PDB Code:2v5z), human AA_2AR (PDB Code:3EML), and human D2R (PDB Code:6CM4) were retrieved from protein Data Bank[15].all water molecules and heteroatom removed and also to add polar hydrogen from the crystal structures was using Bio-Discovery Studio software[16].This modified protein was then saved in .pdb format.

Table 2. Physiochemical properties of Phytochemicals Compounds

Sr. No	Ligand	Physiochemical Properties						
		Mol.Wt (g.mol)	Rotatable Bonds (count)	H Bond Donors	H Bond Acceptors	clogP (approx)	Solubility LogS (ESOL)	TPSA (A^2)
1	Hyoscyamine	289.37	5	1	4	2.06	-2.67	49.77
2	Tropinone	139.19	0	0	2	0.90	-0.92	20.31
3	Hyoscine N Oxide	319.35	5	1	5	-0.07	-2.00	88.49
4	Atropine Oxide	305.37	5	1	4	0.72	-2.46	75.96
5	Cuscohygrine	224.34	4	0	3	1.55	-1.60	23.55
6	Coumarin	146.14	0	0	2	1.82	-2.29	30.21
7	Tropan	125.21	0	0	1	1.72	-1.71	3.24
8	Nicotine	162.23	1	0	2	1.48	-1.89	16.13
9	Acetosyringone	196.20	3	1	4	1.21	-1.31	55.76
10	Acetovanilione	166.17	2	1	3	1.28	-1.43	46.53
11	Acetophenone	120.15	1	0	1	1.82	-2.01	17.07
12	Belladonnine	542.71	7	0	6	4.81	-6.73	59.08
13	Apoatropin	271.35	4	0	3	2.94	-3.72	29.54
14	Methyl Vanillate	182.17	3	1	4	1.47	-2.22	55.76

Table 3: Pharmacokinetic Properties of phytochemicals Compounds

Sr. No	Ligands	HIA	BBB	p-gp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitors	Logkp (skin permeation cm/s)
1	Hyoscyamine	High	Yes	No	No	No	No	Yes	No	-6.77
2	Tropinone	High	No	No	No	No	No	No	No	-6.91
3	Hyoscine N Oxide	High	No	No	No	No	No	No	No	-7.89
4	Atropine Oxide	High	No	No	No	No	No	No	No	-7.20
5	Cuscohygrine	High	Yes	No	No	No	No	No	No	-6.96

6	Coumarin	High	Yes	No	Yes	No	No	No	No	-6.20
7	Tropan	Low	No	No	No	No	No	No	No	-5.84
8	Nicotine	High	Yes	No	No	No	No	No	No	-6.46
9	Acetosyringone									
10	Acetovanilione	High	Yes	No	No	No	No	No	No	-6.95
11	Acetophenone	High	Yes	No	Yes	No	No	No	No	-5.91
12	Belladonnine	High	Yes	No	No	No	Yes	No	Yes	-5.37
13	Apoatropin	High	Yes	No	No	No	No	Yes	No	-5.43
14	Methyl Vanillate	High	Yes	No	No	No	No	No	No	-6.16

Physiochemical and Pharmacokinetic Prediction

SwissADME were used to predict the physiochemical and pharmacokinetic parameters and also check Lipinski rule of five [17].

Retrieval of Ligand

The 3D Structure of Atropa acuminata Compounds were retrieved from the pubchem database. These structures were used for docking studies. The selected 3d structure of the ligands was retrieved from PubChem Compounds database in SDF format and converted to PDBQT after energy minimization using Pyrx and Open Babel Compounds, Molecular formula, and PubChem id of *A. acuminta* present in the study shown in table 1.

Molecular Docking

The behaviour of selected phytochemicals from *A.acuminata* , binding pockets of target protein like MAO-B, AA_2AR and D2R can be described by Molecular docking.to carry out the molecular docking studies, virtual screening software PyRx was used, which is open-source software with an intuitive user interface that runs on all major operating systems. PyRx is a award winning virtual screening software [18] for computational drug discovery that can be used to screen libraries of compounds against potential drug targets. PyRx work is based on empirical binding,free energy scoring and Lamarckian genetic algorithm. All the ligands and macromolecules are converted from pdb to pdbqt format by choosing the autodock option in pyrx. The grid box was centred on the active site of MAO-B, AA_2AR and Dopamine D2R binding affinities were recorded, and top ranked poses were visualized using biovia discovery studio.

Result and discussion

The main objective of this study was exploring the potential of phytochemicals as treatment for Parkinson's disease by examining their interactions with essential proteins involved in the disease. specifically, this study focused on molecular docking 14 Phytochemicals with Monoamine oxidase b , Adenosine A2A Receptor and Dopamine D2 Receptor. The Pharmacokinetic properties of Natural compounds to be considered drug candidates were based on Lipinski's Rule of Five (RO5). the Lipinski rule of five was applied to the 14 selected Phytochemicals using SwissADME software. The results including Lipinski (RO5) and physiochemical properties of the docked compounds, are presented in **Table 2,3**. molecules that violate more than one of these rules many cause bioavailability problems. the entire set of compounds well followed the RO5.Compounds like Tropinone, Hysoscine N Oxide, Atropine oxide and Tropane don't cross the Blood Brain Barrier. BBB pass is a important for brain related disease treatments.

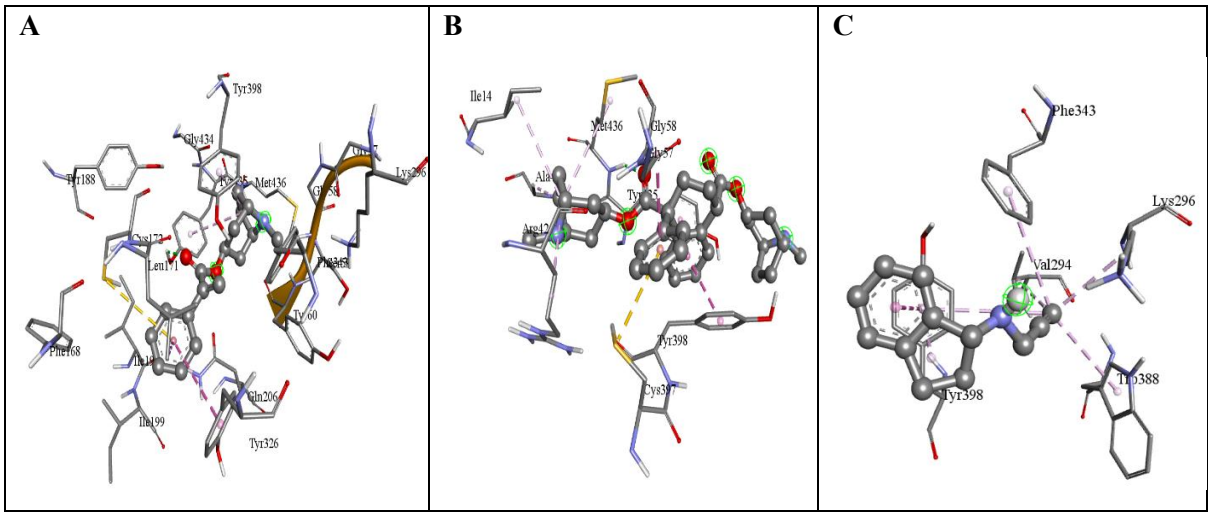
Table 4: Binding affinity of selected Ligands

SR.No	Compound Name	Compound ID	Binding Affinity (Kcal/mol)		
			2V5Z	3EML	6CM4
			Rasagiline (-7.9)	Istradefylline (-6.8)	Ropinirole (-5.9)
1	Hyoscyamine	64692	-8.9	-6.2	-6.9
2	Tropinone	446337	-5.8	-4.6	-4.7
3	Hyoscine N Oxide	3000667	-9.1	-6.1	-6.7
4	Atropine Oxide	3000668	-9.0	-6.5	-6.8
5	Cuscohygrine	1201543	-7.1	-5.2	-5.3
6	Coumarin	323	-7	-5.9	-5.6
7	Tropan	637986	-5.1	-4.7	-4.6
8	Nicotine	89594	-6.3	-5.2	-5.1
9	Acetosyringone	17198	-6.4	-4.7	-5.2
10	Acetovanilione	2214	-6.4	-5.3	-5.4
11	Acetophenone	7410	-5.9	-5.5	-6

12	Belladonnine	442995	**-9.5**	**-8**	**-8.5**
13	Apoatropin	64695	**-9.1**	**-6.7**	**-6.8**
14	Methyl Vanillate	19844	-6.3	-5.4	-5.4

Molecular Docking was employed using PyRx in order to predict the interactions of the protein with its ligands. The binding mode competency of MAO-B, AA_2AR, D2R and the Phytochemicals were investigated via molecular docking.

The Phytochemicals chosen were docked with 20 run and compared with reference like Rasagiline, Istradefyllines and Ropinirole .The Docking energies of the selected Phytochemicals indicated high binding affinities to the target receptor,as shown in Table 4.Among the docked compounds for targets proteins, the top 2 ligands for MAO-B targets(Belldonnine -9.5 kcal/mol and Apotropin -9.1 kcal/mol), AA_2AR (Belldonnine -8 kcal/mol and Apoatropin -6.7 kcal/mol) and D2R (Belldonnine -8.5 kcal/mol and Apotropin -6.8 kcal/mol) were compared with Reference as shown in 2D and 3D structures (Figures 1, 2 and 3).



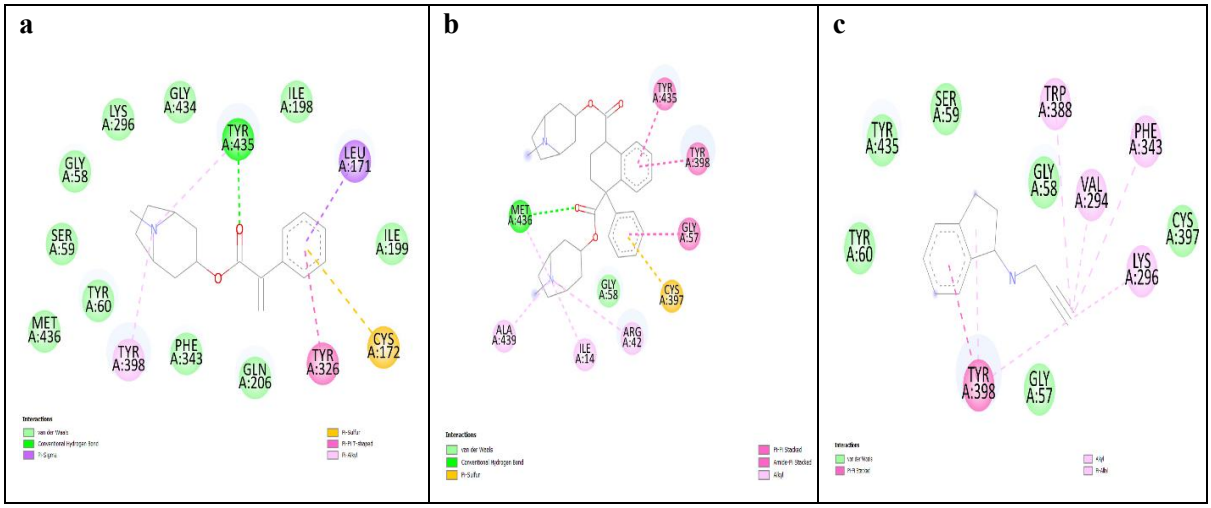


Fig 1: 3D and 2D interaction diagram of top 2 screened ligands(Aa) Apoatropin and (Bb)Belladonnine interacted with MAO-B and (Cc)Rasagiline respectively.

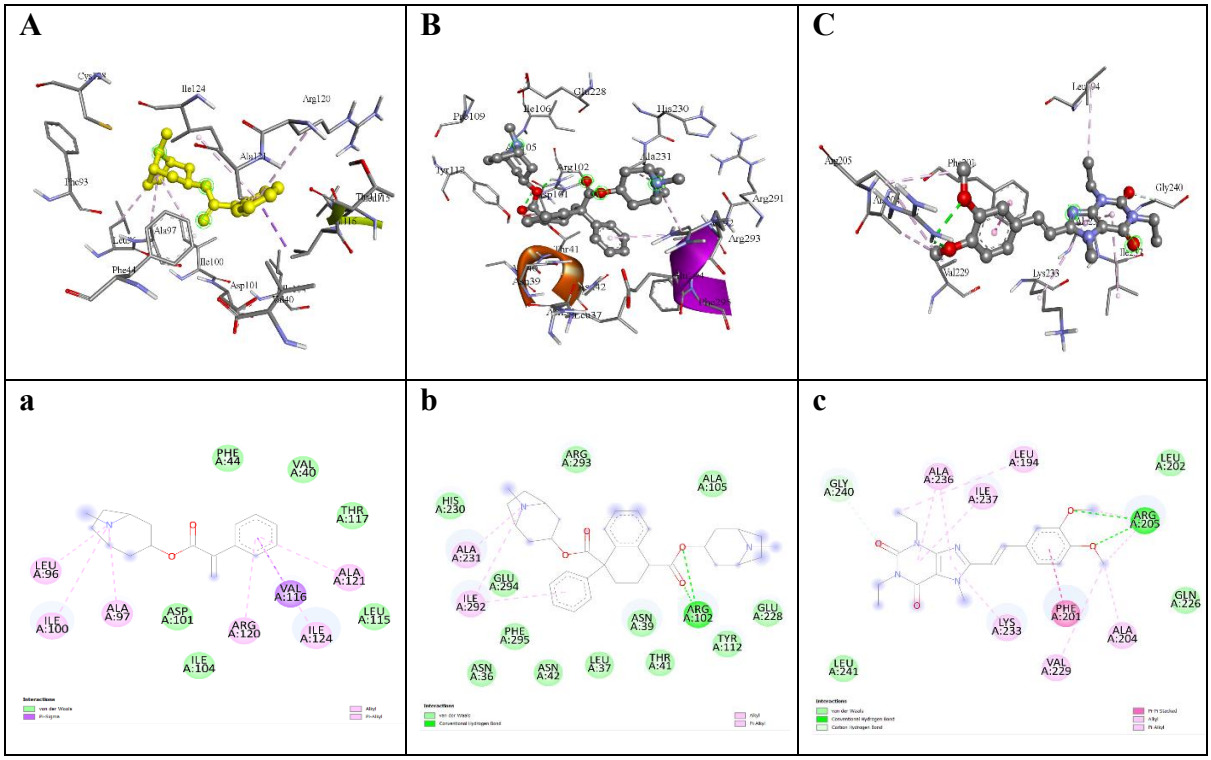


Fig 2: 3D and 2D interaction diagram of top 2 screened ligands(Aa) Apoatropin and (Bb)Belladonnine interacted with MAO-B and (Cc)Istradefylline respectively.

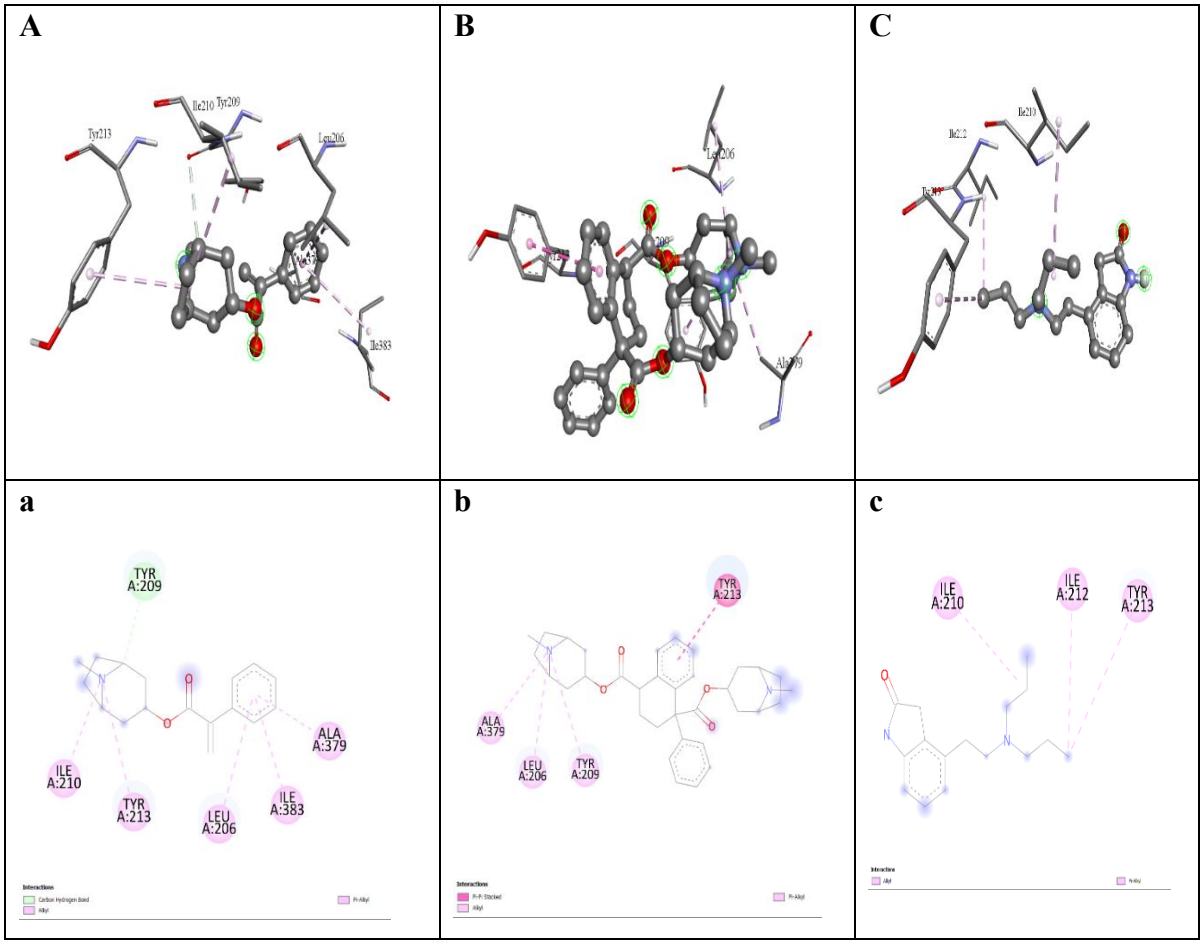


Fig 3: 3D and 2D interaction diagram of top 2 screened ligands(Aa) Apoatropin and (Bb)Belladonnine interacted with MAO-B and (Cc)Ropinirole respectively.

Table 5: Interactive Residues of Target Proteins with Ligands

Ligands	Interacting residues of Target Proteins		
	MAO-B (2V5Z)	**AA2A (3EML)**	**D2R (6CM4)**
Apoatropin (64695)	LEU171,ILE199, CYS172, TYR326,GLN206, PHE343,TYR398, TYR60,MET436,	PHE44,VAL40, TYR117,ALA121, VAL116,LEU115, ILE124,ARG120, ASP101,ILE104,	TYR209, ILE210, TYR213, LEU206, ILE383,

	SER59,GLY58, LYS296,GLY434, TYR435,ILE198	ALA97,ILE100, LEU96.	ALA379.
Belladonnine (442995)	TYR435,TYR398, GLY57,CYS397, GLY58,ARG42, ILE14,ALA439, MET436	ARG293,ALA105, GLU228,ARG102, TYR112,ASN39, THR41,LEU37, ASN42,PHE295, ASN36,GLU294, ILE292,ALA231, HIS230.	TYR213, ALA379, LEU206, TYR209

Bio-Discovery Studio is used for the visualization of the interaction between target proteins and Top 2 phytochemicals and their analysis was done in **Table 5.**

Conclusion

The present study assessed the binding capability of fourteen ligands against multiple protein targets related to Parkinson's disease through molecular docking analysis. Most of the ligands complied with the criteria of Lipinski's Rule of Five, whereas a few compounds showed minor violations that may still be considered acceptable for bioactive molecules. The docking outcomes indicated that several ligands demonstrated favourable binding affinity toward the selected targets. Among these, two ligands exhibited the highest binding affinity and stable interactions with multiple targets, indicating their potential as multitarget therapeutic candidates. The ability to penetrate the Blood–brain barrier is a crucial requirement for the treatment of Parkinson's disease, and the analysis suggested that some ligands may not effectively cross the BBB. Therefore, additional studies are necessary to evaluate the most promising ligands and their target interactions through in vitro and in vivo investigations to validate their therapeutic potential.

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