Evaluation of Neuroprotective Lead Compounds from Capparis moonii Targeting Parkinson's Disease Proteins: A Computational Investigation

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ABSTRACT

Parkinson's Disease (PD) is a chronic and progressive neurodegenerative disorder that has both movement and non-movement related symptoms, primarily caused by loss of dopaminergic neurons, together with multiple pathogenic mechanisms including oxidative stress, mitochondrial dysfunction, neuroinflammation, and protein aggregates. The global elevation in PD burden indicates an immediate requirement for newer and safer therapeutic techniques beyond symptomatic treatments. Natural products possess multi-target therapeutic potential due to their structural diversity, pharmacological versatility, and neuroprotective properties. The fruit of Capparis moonii is a popular traditional medicinal plant used in the treatment of many disorders, which is predominantly attributed to phytochemicals. In the current study, chosen C. moonii extract's phytochemicals were tested employing a structure-based in-silico screening technique against PD-linked target proteins (PDB IDs: 6AFD (DJ-1/PARK7), 5OAT (PINK1), and 9C61 (LRRK2)). Protein structures were retrieved from the Protein Data Bank and prepared using Schrödinger Maestro before docking studies. The docking results demonstrated several compounds that have good binding affinity and a stable binding mode established by important hydrogen bonds and hydrophobic contacts.

Keywords: Parkinson's Disease (PD), Capparis moonii, phytochemicals, molecular docking, ADMET, neuroprotection, DJ-1, PINK1, LRRK2, computational investigation.

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1. INTRODUCTION

Parkinson's Disease (PD) is a chronic neurodegenerative disorder that is considered one of the most common motor-related neurological conditions. Clinically, PD is primarily characterized by motor symptoms like resting tremor, rigidity, bradykinesia, and postural instability (1). In these hallmark motor manifestations of the disease, patients also experience non-motor symptoms, particularly during the early stages of PD, where we can see symptoms like sleep disturbances, autonomic dysfunction, depression, cognitive decline, and sensory abnormalities, which affect the quality of normal life (2). It is primarily characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta of the brain, resulting in impaired dopamine signaling and disruption of the basal ganglia circuitry responsible for coordinating movement of the body (3).

At the molecular and cellular level, PD is observed as a complex disorder with many interlinked pathological pathways and processes. Multiple interconnected mechanisms drive Parkinson's disease, such as oxidative stress, mitochondrial dysfunction, disrupted protein homeostasis, neuroinflammation, and the accumulation of neuronal proteins like α-synuclein in sensitive brain regions (4). These incidents conclude in escalating neuronal impairment, failure in synapses, and finally

lead to neurodegeneration. Because PD is a multifactorial disease, there is a need to target multiple pathogenic pathways has gained increasing attention because single-target intervention might be insufficient for opposing widespread molecular abnormalities associated with the progression of PD (5).

Since Parkinson's disease is becoming more widely reported worldwide, factors such as an ageing population, improved diagnosis, and higher life expectancy have led to higher disability-adjusted life years, which in turn has required increased healthcare expenditure and long-term care (6). Epidemiological assessments showcase that PD is becoming one of the leading contributors to neurological disability worldwide (7). Globally, we can see there are 388,194 fatal cases and 13.35 million incident cases in 2024 across the globe. Between 1990 and 2024, the number of DALYs worldwide attributable to PD decreased from 94.68 to 53.51 per 100,000 people. Age-standardized death rates increased from 2.78 to 4.91 per 100,000 population during the same time, while age-standardized incidence rates grew from 7.82 to 16.92 per 100,000. The excessive SDI area had the greatest PD mortality rate among the 5 SDI zones in 2024 (8). In addition to the direct health burden, PD also contributes to major social and economic challenges due to its chronic nature. The requirement for continuous medication and caregiver dependency among affected individuals further contributes to the significant socioeconomic burden associated with Parkinson's disease (9).

Although several pharmacological therapies are currently available, PD treatment still treats the symptoms rather than the cause. Drugs such as levodopa and dopamine agonists provide significant support in early and moderate stages of the disease; however, long-term therapy is commonly associated with complications such as motor variation, dyskinesias, and reduced responsiveness in patients (10). Therefore, discovering novel therapeutic agents that can target PD-associated molecular pathways remains a critical scientific and clinical priority (11).

In recent years, natural products and plant-derived compounds have gained increasing attention in neurodegenerative research due to their structural diversity, pharmacological versatility, and multi-target potential, with minimal adverse effects during long-term use (12). Phytochemicals, antioxidant-rich constituents, and anti-inflammatories are known to exert neuroprotective effects through reduction of oxidative stress, suppression of inflammatory mediators, and modulation of neuronal survival signaling pathways (13). The characteristics of the natural agents make plant-based bioactive molecules promising candidates for developing new therapeutic agents to fight complex disorders such as PD, Alzheimer's, and other neurodegenerative disorders, where multi-mechanistic intervention may offer improved outcomes of the treatment (14).

Capparis moonii (C. moonii) is a regionally important medicinal plant of India, particularly valued in traditional and healthcare practices of the Western Ghats and its nearby regions (15). Recent studies suggest that Ayurveda is traditionally used to treat respiratory problems, particularly cough and asthma, Liver protection (Kaalameghahi hepatoprotective), ulcers (Kaalameghi ulcer), and as an antioxidant due to its flavonoid content, which includes rutin and quercetin (16). Contemporary studies have validated its anti-inflammatory, antimicrobial properties (demonstrating gastroprotective effects), insulinomimetic activities, and extracts showing potential for treating inflammation, gastric ulcers, as well as possibly some metabolic conditions; it also possesses broad-spectrum antioxidant properties and immunomodulatory effects (17). Therefore, adopting structure-based in-silico approaches, including molecular docking and ADMET/toxicity prediction, offers a rapid and cost-effective strategy to screen large phytochemical libraries, predict ligand–target interactions at the atomic level, and prioritize promising lead candidates for subsequent experimental validation (18).

Thus, here we employed a structure-based in-silico approach for the screening of bioactive phytochemicals from *Capparis moonii* against PD-related target proteins (PDB IDs: 6AFD (DJ-1/PARK7),9C61 (LRRK2), and 5OAT (PINK1) (19). Molecular docking and interaction fingerprinting were carried out to screen the compounds with strong binding poses and favorable interactions relatively at the on-target sites. The top-scoring compounds were further screened. The results of this study could provide a potential basis for subsequent in vivo studies and the design of plant-derived therapeutic agents for PD (20).

2. Materials and Methodology:

2.1. Ligand Dataset Collection

Ligands were selected based on literature, based on their neuroprotective, anti-Parkinson's, antioxidant, and enzyme inhibitory potential, with emphasis on phytochemicals derived from *Capparis moonii* (21). In addition, the ligand dataset was compiled from previously published phytochemical profiling and pharmacological studies of *Capparis moonii*, ensuring that only reported plant-derived constituents were included for screening. The corresponding compound structures were retrieved from publicly available chemical databases such as PubChem and downloaded in standard formats (SDF) for further processing. The selected ligands were 1,3,6-tri-O-galloyl-beta-D-glucose (PubChem ID:452707), Icariin (PubChem ID:5318997), Nardosinone (PubChem ID:168136), baicalein

(PubChem ID:5281605), stachydrine (PubChem ID:115244), and beta-Asarone (PubChem ID:5281758). Levodopa (Pubchem ID:6047) is considered standard (21).

2.2. ADMET Prediction

The shortlisted *Capparis moonii* phytochemical ligands were further evaluated for drug-likeness and predicted pharmacokinetic suitability to support lead identification using pkCSM. Additional descriptors, MW (g/mol), Water solubility, hERG I inhibitor, hERG II inhibitor, Hepatotoxicity, Total Clearance, Skin Permeability, BBB Permeability, CNS permeability (22). ADMET profiling was carried out to predict oral absorption, bioavailability, and overall pharmacokinetic behavior, while toxicity risk and safety alerts were screened where applicable. Ligands meeting acceptable drug-likeness and ADMET criteria were considered promising candidates for further experimental validation (23).

2.3. Ligand preparation:

Ligand preparation was carried out using the ligprep module in Maestro v 13.7 to ensure correct molecular geometry and chemically relevant states before docking, including conversion to optimized three-dimensional structures, generation of ionization states at physiological pH, generation of tautomers and stereoisomers where applicable, and geometry optimization through energy minimization. Duplicate entries and chemically inconsistent structures were removed, and the final curated ligand library was saved in a docking-compatible format for subsequent docking studies (24).

2.4. Selection and Retrieval of PD Protein Targets from the Protein Data Bank (PDB)

In this in-silico study, PD-associated protein targets were selected for structure-based drug discovery based on the availability of experimentally validated three-dimensional structures and their suitability for molecular docking analysis. The selection criteria included structural completeness, presence of a well-defined binding cavity, and compatibility with computational screening workflows. Based on these, two receptor proteins were finalized: PDB ID: 6AFD (DJ-1/PARK7) and PDB ID: 5OAT (PINK1),9C61 (LRRK2) (25)(26)(27). The corresponding crystal structures were obtained from the RCSB Protein Data Bank (PDB) and downloaded in PDB format, which were then used as receptor models for subsequent protein preparation, active site mapping, and docking simulations (28).

2.5. Protein Structure Preparation and Active Site Prediction with Grid Box Generation

The retrieved protein structures (PDB ID: 6AFD (DJ-1/PARK7) and 5OAT(PINK1),9C61 (LRRK2)were prepared using the Schrödinger Suite (version 14.4) by removing crystallographic water molecules and non-essential heteroatoms, followed by the addition of hydrogen atoms and assignment of appropriate atomic charges to ensure correct protonation and docking compatibility, while Energy minimization was not performed was performed to optimize the protein geometry and eliminate steric clashes; subsequently, the receptor binding pocket was identified based on available structural information, and the docking grid box was generated by selecting suitable centroid coordinates and grid dimensions to completely enclose the predicted active site for efficient ligand sampling during molecular docking simulations (29).

2.6. Molecular Docking

Prepared *Capparis moonii* phytochemical ligands were docked into the active-site binding pocket of the prepared target proteins using the Glide module of Schrödinger Maestro to predict ligand binding orientation and estimate binding affinity. Docking results were generated as multiple binding poses and ranked based on docking score, pose alignment within the binding cavity, and binding stability supported by key residue interactions at the active site. Ligands showing strong and consistent binding profiles were shortlisted, and selected complexes were validated using docking predictions to identify the most stable ligand–protein interactions (30).

2.7. Molecular dynamics (MD) simulations

Molecular dynamics (MD) simulations were carried out using the Desmond module of the Schrödinger suite to analyze the stability of the protein-ligand complexes. The docked complexes of the target protein (PDB ID: 9C61) with the standard drug Levodopa and the chosen lead compound 1,3,6-tri-O- galloyl-β-D-glucose were used as the initial structures. The system was set up using the System Builder tool by placing the complex inside an orthorhombic box of size 10×10×10 Å with the TIP3P water model, with a 10 Å buffer distance from the protein surface. The system was neutralized by adding appropriate counter ions, and 0.15 M NaCl was added to mimic physiological conditions. Energy minimization was carried out to remove steric clashes and optimize the system geometry (31).

3. Results:

3.1. Ligand Dataset Collection and Preparation

The phytochemicals of *Capparis moonii* that have been screened are flavonoids, phenolic compounds, alkaloids, and terpenoids. The molecular weights of compounds such as Icariin and 1,3,6-tri-O-galloyl-beta-D-glucose (TGG) are relatively higher, indicating the presence of multiple functional groups that can increase binding interactions. The molecular weights of compounds such as Stachydrine and Beta-Asarone are relatively lower and can have better bioavailability. The addition of Levodopa as a standard compound will enable the comparison of binding efficiency and pharmacological relevance.

Table 1. List of *Capparis moonii* phytochemicals screened

Sl. No	Compound Name	PubChem CID	Molecular Formula	Molecular Weight g/mol
1	1,3,6-tri-O-galloyl-beta-D-glucose	542707	C27H24O18	636.5 g/mol
2	Icariin	5318997	C33H40O15	676.7 g/mol
3	Nardosinone	168136	C15H22O3	250.33 g/mol
4	baicalein	5281605	C15H10O5	270.24 g/mol
5	stachydrine	115244	C7H13NO2	143.18 g/mol
6	beta-Asarone	5281758	C12H16O3	208.25 g/mol
7	Levodopa (Standard)	6047	C9H11NO4	197.19 g/mol

Totally six phytochemicals from *Capparis moonii* were selected and screened for in-silico analysis, along with Levodopa, which is used as a standard reference drug. The compounds were accessed from PubChem, and they represented diverse chemical classes with molecular weights ranging from 143.18 to 676.7 g/mol. This diversity provides a bigger ligand dataset for evaluating drug-likeness and target binding potential against Parkinson's disease-related proteins.

3.2. ADMET Profiling of Selected Phytocompounds

Figure 1: ADMET profile of selected phytochemicals from *Capparis moonii*

Compound Name	MW (g/mol)	Water solubility	hERG I inhibitor	hERG II inhibitor	Hepatotoxicity	Total Clearance	Skin Permeability	BBB Permeability	CNS permeability
1,3,6-tri-O-galloyl-beta-D-glucose	636.471	-2.892	No	Yes	No	0.417	-2.735	-3.569	-5.183
Icariin	676.668	-2.965	No	Yes	No	-0.04	-2.735No	-2.138	-4.819
Nardosinone	250.338	-3.486	No	No	No	1.199	-2.953	0.488	-2.812
baicalein	270.24	-3.302	No	No	No	0.252	-2.735	-1.061	-2.21
stachydrine	143.186	0.19	No	No	NO	0.612	-2.778	-0.197	-2.959
beta-Asarone	208.257	-2.536	No	No	No	0.441	-1.885	0.229	-1.993
Levodopa (Standard)	197.19	-2.89	No	No	Yes	0.43	-2.735	-0.843	-3.032

3.2.1. 1,3,6-tri-O-galloyl-β-D-glucose

The compound has displayed an overall acceptable safety profile, and it has no predicted hepatotoxicity or negative hERG I inhibition. Yet it has shown very poor BBB and CNS permeability, which suggests minimal brain penetration. Therefore, even though it may offer some overall benefits, it may not be suitable as a main treatment option for targeting the central nervous system in Parkinson's disease.

3.2.2. Icariin

This compound shows good, predicted liver safety and no hERG I inhibition, but it has poor BBB and CNS permeability, indicating weak brain availability. Added to this, the hERG II inhibition warning may increase concerns related to cardiac safety. Overall, this compound appears to be more suitable for peripheral protective effects other than direct CNS-mediated anti-Parkinson activity.

3.2.3. Nardosinone

This compound appears to give one of the most promising outcomes because of this favoring nature towards BBB permeability and relatively improved CNS penetration. It also has a clean safety profile with no hERG inhibition and no hepatotoxicity prediction. Altogether, this compound stands out as a strong CNS-relevant candidate among the tested phytocompounds for Parkinson's-related targeting.

3.2.4. Baicalein

This compound also shows a postive favourable predicted safety outcome with no hepatotoxicity and no hERG inhibition. It has a moderate BBB and CNS permeability, indicating limited but possible brain entry. Overall, this compound can act as a supportive neuroprotective candidate, even though it may not be as strong as the best-performing ligands in the dataset for CNS delivery.

3.2.5. Stachydrine

This compound also has a strong safety outcome with no predicted hepatotoxicity and no hERG inhibition. But the BBB and CNS permeability are low, which suggests poor brain penetration. Apart from that, it can more likely offer general protective activity rather than acting as a direct CNS-targeted compound for Parkinson's disease therapy.

3.2.6. β-Asarone

This compound has demonstrated one of the best outcomes among all compounds, by showing very good BBB permeability and the highest CNS permeability in the dataset. It also carries a safe profile with no predicted hepatotoxicity and no hERG inhibition. Bringing together, this compound appears highly promising as a CNS-active phytocompound for Parkinson's disease targeting.

3.2.7. Levodopa (Standard)

Levodopa is a very effective reference compound, but in our prediction, it has safety screening limitations, as it appears that in silico prediction suggested a potential hepatotoxicity alert, which requires further experimental verification. It also suggests a weaker passive penetration as it shows comparatively low BBB and CNS permeability values. Brought together, it functions well as a

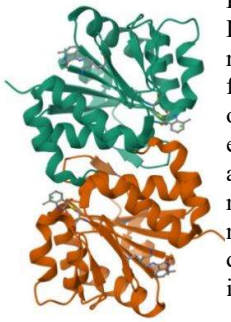
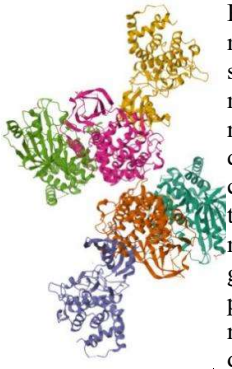
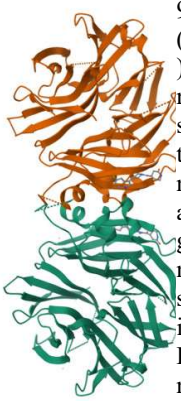
standard drug but highlights the need for safer CNS-penetrating alternatives.

3.3. Selection and Retrieval of PD Protein Targets from the Protein Data Bank (PDB)

The crystal structures for 6AFD (DJ-1/PARK7) and 5OAT (PINK1),9C61 (LRRK2) were taken from the RCSB Protein Data Bank, and then ran some quick validation checks to make sure they are suitable for docking. For the enhancement of the structure, hydrogens were incorporated, which fixed the bond orders and adjusted the protonation states, so everything appeared normal. The two proteins had ligands already bound to them, and the compounds demonstrated that it was easier due to the actual binding sites. These targets are relevant to Parkinson's disease.

From all the compounds screened, β-asarone and nardosinone showed better performance. They were easily able to get into the brain, didn't affect the liver, and didn't block hERG channels, so they look like strong options for Parkinson's disease. On the other hand, icariin and 1,3,6-tri-O-galloyl-β-D-glucose just don't cross the blood-brain barrier well, and levodopa came up with a possible risk for liver toxicity. So, this supported the need for safer CNS drugs.

Table 2: Target protein details

PDB ID		Structure of Protein	Function
6AFD (DJ-1/PARK7)			DJ-1 Protects neurons from oxidative stress and mitochondrial dysfunction
5OAT (PINK1)			PINK maintains mitochondrial quality control through mitophagy, protecting dopaminergic neurons.
9C61 (LRRK2)			9C61 (LRRK2) regulates vesicle trafficking, autophagy, and neuronal survival in Parkinson's.

3.4. Docking Score of *Capparis moonii* Extract Ligands Against PD Targets

3.4.1. Target 9C61 (LRRK2)

The molecular docking analysis shows that TGG had the highest binding affinity with a docking score of -9.353 kcal/mol and formed 11 hydrogen bonds, which clearly indicates a strong and stable binding interaction with the PD target protein (9C61 (LRRK2)). Icariin also had a substantial binding affinity of -8.396 kcal/mol with five hydrogen bonds. Moderate binding interactions were observed for Nardosinone, Baicalein, and Levodopa (standard)-6.103 kcal/mol, and it has 4 hydrogen bonds, whereas Stachydrine and Beta-Asarone had relatively lower binding affinities. Based on the docking analysis, it can be concluded that the chosen phytocompounds, namely TGG and Icariin, may possess promising inhibitory potential against the PD target.

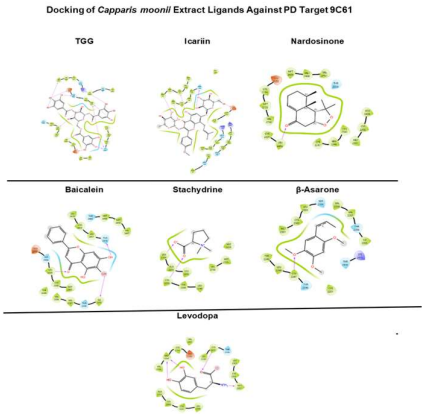


Figure 2: Docking Score of *Capparis moonii* Extract Ligands Against PD Target 9C61 (LRRK2).

3.4.2. Target PINK1 (5OAT)

The docking analysis against the 5OAT (PINK1) target protein shows that 1,3,6-tri-O-galloyl-beta-D-glucose exhibited the highest binding affinity –6.306 kcal/mol with 5 hydrogen bonds, indicating a stable interaction. Beta-Asarone and Levodopa (standard) –5.288 kcal/mol with 3 hydrogen bonds

demonstrated comparable docking scores, suggesting moderate binding potential. Icariin formed the highest number of 7 hydrogen bonds, despite a relatively lower docking score. Overall, the results indicate that selected phytocompounds from *Capparis moonii* may interact effectively with 5OAT (PINK1) (PINK1), highlighting their possible role in neuroprotective mechanisms.

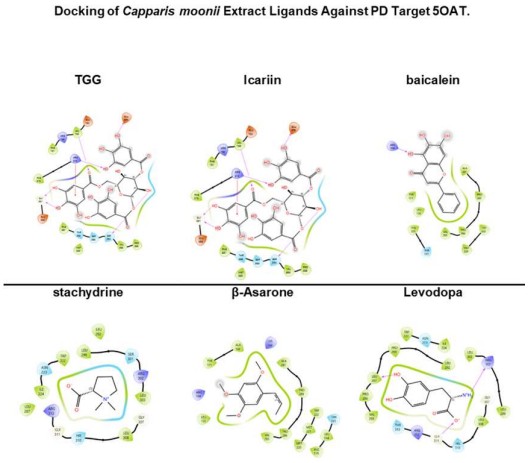


Figure 3: Docking Score of *Capparis moonii* Extract Ligands Against PD Target 5OAT (PINK1).

3.4.3. Target 6AFD (DJ-1/PARK7)

Highest binding affinity was achieved by Levodopa (standard) (–5.026 kcal/mol) with 4 hydrogen bonds, confirming it as the strongest binder for this protein. Among the phytocompounds, 1,3,6-tri-O-galloyl-β-D-glucose (–4.563 kcal/mol) and stachydrine (–4.503 kcal/mol) were the better performers, but overall interactions were weaker compared to 9C61 (LRRK2).

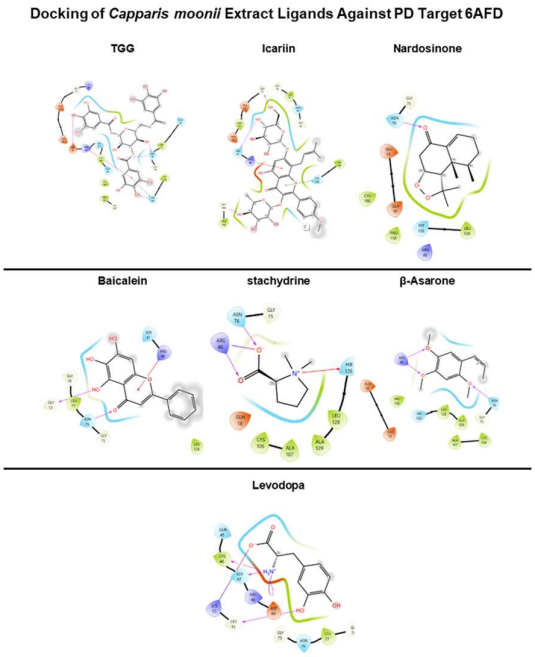


Figure 4: Docking Score of *Capparis moonii* Extract Ligands Against PD Target 6AFD (DJ-1/PARK7).

Highest binding affinity was achieved by Levodopa (standard) (–5.026 kcal/mol) with 4 hydrogen bonds, confirming it as the strongest binder for this protein. Among the phytocompounds, 1,3,6-tri-O-galloyl-β-D-glucose (–4.563 kcal/mol) and stachydrine (–4.503 kcal/mol) were the better performers, but overall interactions were weaker compared to 9C6

3.4.4. Molecular Dynamics Simulation

The 300 ns molecular dynamics simulation confirmed the stability of both protein–ligand complexes. TGG exhibited stable binding with a protein RMSD of 2.5–3.0 Å and ligand RMSD of 5–6 Å, indicating conformational flexibility within the binding pocket, whereas Levodopa showed greater stability with a protein RMSD of 2.1–2.4 Å and ligand RMSD of 1.0–1.8 Å, maintaining consistent interactions throughout the simulation.

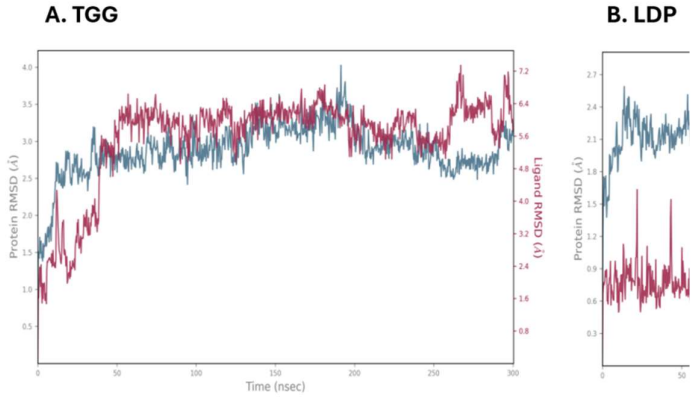


Figure 5: Protein–ligand RMSD plots of the protein–TGG (left) and protein–Levodopa (right)

complexes during a 300 ns molecular dynamics simulation. The protein backbone remained stable throughout the simulation, while TGG exhibited higher ligand fluctuations than Levodopa, indicating greater conformational flexibility within the binding pocket.

3.5. Discussion:

Docking analysis of *Capparis moonii* phytocompounds against Parkinson's disease targets (9C61 (LRRK2) ,5OAT (PINK1), and 6AFD (DJ-1/PARK7) revealed clear differences in binding strength across proteins. Target 9C61 (LRRK2) showed the strongest overall interactions, with 1,3,6-tri-O-galloyl-β-D-glucose producing the best docking score of –9.353 kcal/mol and maximum hydrogen bonding with 11 bonds, indicating a highly stable complex. The results, it showed that 9C61 (LRRK2) can be a highly responsive target for polyphenolic phytocompounds among the six phytocompounds. PINK1 also preferred the same ligand with a docking score of –6.306 kcal/mol and 5 H-bonds, which validates its potential role in mitochondrial quality control related to Parkinson's pathways. Yet, 6AFD (DJ-1/PARK7) showcased lower docking scores compared to the other genes. The molecular dynamics simulation supported the docking results, demonstrating stable binding of TGG within the protein binding pocket throughout the 300 ns simulation. Despite moderate ligand fluctuations, persistent interactions were maintained, indicating favorable complex stability. The best binding was achieved by Levodopa with a docking score of -5.026 kcal/mol, confirming it as a reliable standard reference compound in this dataset. Overall, the results highlight 1,3,6-tri-O-galloyl-β-D-glucose as the most effective multi-target lead against 9C61 (LRRK2) and 5OAT(PINK1), while 6AFD (DJ-1/PARK7) appears less sensitive to the selected phytocompounds. These findings support further validation using molecular dynamics and experimental assays.

3.6. Conclusion:

This in-silico screening of *Capparis moonii* phytochemicals brought six different bioactive compounds, plus Levodopa as a standard for comparison. All the compound structures were taken from PubChem, and we can see their molecular weights ranged from 143.18 to 676.7 g/mol. β-asarone and nardosinone showed good results in the pharmacokinetic side. They both crossed the blood-brain barrier (BBB) and got into the central nervous system (CNS), as well as per the outcome. They also didn't show signs of being toxic for liver and interfering with hERG channels. Therefore, β-asarone and nardosinone look like better options for targeting Parkinson's disease. Although TGG exhibited superior docking scores, its poor BBB and CNS permeability may limit its direct application as a CNS therapeutic. Similarly, icariin demonstrated limited brain penetration, and levodopa showed a potential hepatotoxicity risk in silico. The molecular docking results added information on the compounds, and they all didn't bind the same way to the main Parkinson's disease targeted proteins like 9C61 (LRRK2), 5OAT (PINK1), and 6AFD (DJ-1/PARK7). 1,3,6-tri-O-galloyl-β-D-glucose came out on top there (–9.353 kcal/mol) and had the strongest binding overall, forming the most hydrogen bonds, and it also bound stably to PINK1. On the other hand, 6AFD (DJ-1/PARK7) did not show a strong binding affinity, but Levodopa showed the best performance against the target.The molecular dynamics simulation confirmed the stability of both protein–ligand complexes, with TGG demonstrating stable binding and sustained interactions comparable to the standard drug Levodopa throughout the 300 ns simulation period. Therefore, these C. moonii compounds demonstrated promising lead potential that can be a multi-target. These findings need further investigation using molecular dynamics simulations and experimental validation.

3.7.

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