Pharmacogn. Res., 2027; 19(1):329-337.
https://www.phcogres.com

Original Article

Identification of Potential Plant-Based Bioactive Compounds as α-Synuclein Targets via Molecular Docking and Molecular Dynamics Simulations

Nivetha Rajendiran[1], Kannan Muthu[2], Gowdham Manivel[3], Ethirajan Sukumar[4], Senthilkumar Sivanesan[5,*]

[1]Department of Biotechnology, Saveetha School of Engineering, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, INDIA.
[2]Department of Bioinformatics, Saveetha School of Engineering, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, INDIA.
[3]Chemomicrobiomics Laboratory, KMCH Research Foundation, Coimbatore, Tamil Nadu, INDIA.
[4]Division of Research and Development, VPro Biotech, Arumparthapuram, Puducherry, INDIA.
[5]Department of Research and Development, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, INDIA.

ABSTRACT

Introduction: Parkinson's Disease (PD) is a distressing neurodegenerative ailment that involves the demise of neurons present in dopaminergic system and continuous progression of α-synuclein into amyloid fibrils. Combating α-synuclein aggregation represents an intriguing approach to develop disease-modifying therapy. **Materials and Methods:** This work encompasses a systematic *in silico* design to evaluate plant-based benzoquinone and its derivatives Vilangin, phenyl-Vilangin, and methyl-Vilangin, against the α-synuclein fibril structure (PDB ID: 2N0A). Molecular docking was performed at three reported functional binding pockets (Sites 2, 3/13, and 9) to determine the binding affinity and interaction profiles. The most promising complexes were subsequently subjected to 200-ns molecular dynamics simulations using the CHARMM force field. The root mean square deviation, the root mean square fluctuation, principal component analysis, and free energy landscape profiling were used to evaluate structural stability and conformational behaviour. **Results:** The docking results identified phenyl-Vilangin as the strongest binder, particularly at Site 3/13 (ΔG=-7.9 kcal/mol), followed by vilangin, while methyl-vilangin showed comparatively weaker interactions. Molecular dynamics simulations confirmed enhanced structural stabilisation in the α-synuclein-phenyl-vilangin complex, characterised by lower conformational deviation, reduced residue-level fluctuations, restricted essential motions, and well-defined low-energy conformational basin. **Conclusion:** Overall, phenyl-vilangin emerged as the most promising scaffold for targeting α-synuclein aggregation, warranting further experimental validation.

Keywords: Anti-Parkinsonian Agent, α-synuclein, Methyl-vilangin, Molecular docking and dynamics simulations, Phenyl-vilangin, Vilangin.

Correspondence:
Dr. Senthilkumar Sivanesan
Department of Research and Development, Saveetha Institute of Medical and Technical Sciences, Chennai, Tamil Nadu, INDIA.
Email: senbio@gmail.com
ORCID: 0000-0001-5133-7090

Received: 12-06-2026;
Revised: 24-07-2026;
Accepted: 01-09-2026.

INTRODUCTION

Parkinson's Disease (PD) is a long-lasting and detrimental neurodegenerative ailment that affects the Central Nervous System (CNS). It involves the incessant injury of dopaminergic neurons in the Substantia Nigra Pars Compacta (SNpc) and the development of Lewy Bodies (LBs), which results in dopamine insufficiency in the basal ganglia thereby manifesting both motor and non-motor symptoms (Wardhan *et al.*, 2024). The frequency of PD increases with age, and the disease affects millions of people throughout the world. Moreover, epidemiological observations indicate a higher occurrence in men than in women (Thangavelu *et al.*, 2024). Pathologically, PD is strongly linked with the aggregation of α-synuclein (α-syn) in LBs and Lewy neurites. Tremor, rigidity, bradykinesia, constipation, hyposmia, depression, sleep instabilities including rapid eye movement sleep related disorder, and other clinical manifestations are frequently reported in PD (Negi *et al.*, 2024). Evidence suggests that misfolded or aggregated α-syn may originate in peripheral tissues viz., the gastrointestinal tract and propagate via neural pathways such as the vagus nerve to the brainstem. This is supported by other clinical manifestations, among which gastrointestinal dysfunction, especially constipation, may appear prior to classical motor symptoms (Adam *et al.*, 2024). The progressive spread of α-syn inclusions across brain regions is considered a major

OPEN ACCESS

Manuscript TECHNOMEDIA

DOI: 10.5530/pres.20270200

Copyright Information :
Copyright Author (s) 2027 Distributed under Creative Commons CC-BY 4.0

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

neuropathological basis of disease progression, emphasising that α-syn assembly is not only as a biomarker for diagnosis and staging but also as a promising target for therapeutic intervention (Endo *et al.*, 2024).

Under physiological settings, α-syn, which comprises 140 amino acids, is an intrinsically disordered protein and contains an apparent lipid-binding domain at its N-terminus. The highly hydrophobic segment (residues 65-90), also referred to as the Non-Amyloid β Component (NAC), plays a key role in α-syn load and fibril formation (Sardar *et al.*, 2018). The unusual accumulation of α-syn and the subsequent neurotoxicity contribute to the worsening of dopamine-producing neurones in the SNpc, thereby impairing motor control and related neural functions (Poewe *et al.*, 2017).

Most PD cases are considered idiopathic; however, both genetic predisposition and environmental exposures are known to contribute to disease risk. Several studies suggest that interaction with pesticides, herbicides, and heavy metals may upsurge the risk of PD, while lifestyle factors such as cigarette smoking and excessive caffeine consumption have been associated with a lower risk as per epidemiological reports (Kouli *et al.*, 2018). The development and progression of PD involve complex interactions among genes, proteins, cellular pathways, dysfunctional organelles, and neural networks, which may explain the heterogeneity of symptoms and disease trajectories among patients (Elkouzi *et al.*, 2019). Although dopaminergic therapies remain the clinical gold standard to hamper the symptoms of PD, there is still a significant unmet need for therapies that address dopaminergic-resistant motor and non-motor symptoms and, importantly, modify the natural course of disease progression. In recent decades, many candidates' disease-modifying agents have not achieved the primary endpoints in clinical trials (Lang and Espay, 2018). Current therapies such as levodopa, selegiline, syndopa, biperiden, and bromocriptine primarily aim to restore physiological balance and manage symptoms. However, their long-term use may cause adverse effects and reduced efficacy in controlling disease progression (Alimohammadi *et al.*, 2021; Vidović and Rikalovic, 2022). Hence, there remains a strong need to identify and validate new molecular scaffolds that can modulate PD-relevant targets, especially α-syn aggregation.

Benzoquinone derivatives have emerged as promising candidates in PD-related research. (Koppal *et al.*, 2021; Ramachandra *et al.*, 2022). Being a naturally occurring benzoquinone compound, embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone) is easily extracted from the berries of the *Embelia ribes* plant and widely investigated in PD models as protective agent. It has revealed encouraging therapeutic potential in both *in vitro* and *in vivo* studies. Our recent published cell line study supports the *in vitro* efficacy of vilangin (embelin dimer) against rotenone toxicity in SHSY cells (Rajendiran *et al.*, 2026). Computational mapping has reported multiple potential binding sites on α-syn fibrils, with Sites 2, 3/13, and 9 as favourable pockets for ligand binding (Ramachandra *et al.*, 2022). Additionally, embelin has been reported to influence mitochondrial biogenesis and to modulate NAD/NADH levels in dopaminergic neuronal cell systems (Rao *et al.*, 2020). Based on these results, the present study employed a structured *in silico* strategy to examine the binding of vilangin, phenyl-vilangin, and methyl-vilangin to α-syn. Molecular docking was used to identify the optimal interaction partners, and their binding affinities and modes were assessed. The GROMACS program was used for Molecular Dynamics (MD) simulations to decode the protein-ligand interactions (Nieto-Giraldo *et al.*, 2026). Principal Component Analysis (PCA) and Free Energy Landscape (FEL) analysis clarified the dynamic behaviour of the complexes as well as the effect of ligand binding on α-syn activity (Papaleo *et al.*, 2009).

MATERIALS AND METHODS

Molecular Docking

The Three-Dimensional (3D) structure of the α-syn fibril (PDB ID: 2N0A) (Figure 1(A)) (Ramachandra *et al.*, 2022) was retrieved from the RCSB Protein Data Bank. AutoDock Vina (version 1.2.0) was used to assess the binding affinity and interaction profiles of α-syn and three derivatives of embelin (Figure 1B): vilangin (Figure 1C), phenyl vilangin (Figure 1D), methyl vilangin (Figure 1E). Based on prior structural and experimental evidence, three functionally relevant binding regions - Sites 2, 3/13, and 9 - were selected as docking targets.

Ligand structures were constructed using ChemAxon Marvin 17.21.0 and subjected to geometry optimisation in Avogadro 1.2.0. Protein and ligand preparation, including the addition of polar hydrogens and assignment of partial charges, was performed using OpenBabel, and the files were converted to the PDBQT format. Docking grid boxes were defined to fully encompass each binding site, ensuring unrestricted ligand accessibility. Docking exhaustiveness values were set within the recommended ranges to achieve robust conformational sampling. The most favourable binding poses were selected based on minimum binding free energy and analysed for key intermolecular interactions using UCSF Chimaera.

MD Simulations

MD simulations were executed using GROMACS 2023.2 (Nieto-Giraldo *et al.*, 2026) to assess the structural stability and dynamic behaviour of the top-ranked α-syn complexes with vilangin and phenyl-vilangin. The CHARMM36 force field was employed for protein and ligand parameterisation. TIP3P water molecules were used to solvate each compound in a cubic simulation box while keeping a minimum of 0.1 nm between the protein surface and the box boundary. To neutralize the system, counterions were introduced.

The steepest descent algorithm was ensured to minimize energy, followed by conjugate gradient minimisation to eliminate steric clashes. System equilibration was carried out in two stages: NVT equilibration with a V-rescale thermostat at 300 K (Martonák *et al*., 2003) and NPT equilibration with the Parrinello-Rahman barostat at 1 bar. The protein backbone was subjected to positional restrictions during each 500ps equilibration phase (De Sancho, 2022). Subsequently, a 200-ns production MD simulation was executed without restraints. Trajectories were recorded at 10-ps intervals and analysed based on the Root Mean Square Deviation (RMSD), the Root Mean Square Fluctuation (RMSF), and essential dynamics.

PCA and FEL Analysis

PCA was applied to characterise the leading collective motions of the α-syn-ligand complexes by diagonalising the covariance matrix of atomic fluctuations (Papaleo *et al*., 2009). The most important structural changes in a protein are captured by the first eigenvector of the mass-weighted covariance matrix. However, the first eigenvector frequently shows a cosine distribution near 1, indicating large-scale motions that are not helpful for understanding protein activity in terms of the free energy landscape (Maisuradze and Leitner, 2007). The cosine content of each Principal Component (PC) was calculated to assess trajectory convergence and to ensure reliable FEL construction. Components with cosine content values ≤ 0.2 were selected to generate the FEL, representing meaningful conformational sampling. The *g_sham* tool was used to compute the FEL, enabling identification of stable conformational basins and ligand-induced stabilisation effects (Samantaray *et al*., 2025).

Statistical Analysis of Molecular Dynamics Trajectories

The stability and dynamic behavior of the simulated complexes were evaluated using several trajectory-based metrics implemented in GROMACS 2023. Structural stability throughout the simulation was assessed using Root Mean Square Deviation (RMSD), whereas residue-level flexibility was analyzed using Root Mean Square Fluctuation (RMSF). The temporal evolution of these parameters was monitored across the entire 200 ns simulation period. For PCA, the significance of each principal component was determined from the associated eigen values obtained from the covariance matrix. Trajectory convergence was statistically validated by calculating the cosine content (ci) for the first 20 principal components. Principal components with ci values ≤ 0.2 were considered sufficiently converged and were selected for subsequent free energy landscape analysis. The resulting FELs were interpreted based on the distribution of energy minima and conformational basins, with lower-energy regions representing thermodynamically stable conformational states.

RESULTS

Molecular Docking Analysis and Binding Site Evaluation

Molecular docking was employed as the primary screening strategy to estimate the binding affinity and interaction profiles of vilangin, phenyl-vilangin, and methyl-vilangin to the α-syn fibril. Docking simulations were performed at three previously reported and functionally relevant binding pockets, namely Sites 2, 3/13, and 9, to identify the most favourable ligand-site combinations and prioritise candidates for MD simulations.

The docking result showed distinct variations in ligand binding to each site in α-syn (Table 1 and Figure 2a), suggesting that both pocket microenvironment and ligand structure are important factors in controlling binding affinity. Phenyl-vilangin has the highest binding affinity at Site 3/13 among all site-ligand combinations, with a projected inhibition constant (Ki) of 1.617 nM and a binding free energy (ΔG) of -7.9 kcal/mol. This interaction is the most energetically favourable in the present study. The favourable binding of phenyl-vilangin can be explained by its phenyl substitution, which allows for more hydrophobic and π-stacking interactions in the β-sheet-rich area of the α-syn fibril.

Vilangin shows favourable binding properties, especially at Sites 2 (ΔG=-6.7 kcal/mol; Ki=12.256 nM) and 3/13 (ΔG=-6.2 kcal/mol; Ki=28,504 nM). Vilangin presents favourable contacts with Gly41 and His50, hydrophobic interactions with Phe4, and stable hydrogen bonds with the side chains of Lys43 and Lys45 at Site 2. These interactions confirm previous reports that have identified Site 2 as a functionally relevant area for small-molecule binding and successfully anchor the ligand within the binding pocket. Vilangin appears to have sufficient structural complementarity to sustain stable occupancy at this location based on the combination of polar and non-polar contacts.

Compared with vilangin and phenyl-vilangin, methyl-vilangin consistently demonstrates decreased binding at all sites, including an unfavourable interaction at Site 9. The main reason for this decreased affinity is the lack of important stabilising interactions, such hydrogen bonding and aromatic stacking, which lead to poor complementarity with the binding pockets. This observation aligns with the structure-activity relationship trends observed for α-syn ligands, where successful binding is mostly dependent on aromaticity and hydrogen-bonding capability.

Taken together, the molecular docking analysis clearly indicates that phenyl-vilangin (Site 3/13) is the top candidate, with vilangin (Site 2 and Site 3/13) emerging as a promising secondary lead (Figure 2b). Based on these results, vilangin and phenyl-vilangin were selected for further validation based on long-timescale MD simulations.

MD Simulations: Structural Stability and Conformational Behaviour

To ensure the molecular docking predictions and to monitor the dynamic stability of the protein-ligand complexes, 200-ns MD simulations were run for α-syn coupled to vilangin and phenyl-vilangin. CHARMM36 force field were employed to run the simulations, with trajectory analyses focused on the RMSD (Figure 3A) and the RMSF (Figures 3B and 3C), as well as PCA and FEL profiling.

RMSD Analysis

RMSD analysis demonstrates the global conformational stability of protein-ligand complexes over the course of the simulation. As presented in Figure 4a, both the vilangin and phenyl-vilangin systems show an initial equilibration phase, followed by convergence into stable trajectories, indicating successful system relaxation. Interestingly, throughout the production cycle, the α-syn-phenyl-vilangin complex consistently presents a lower RMSD than the α-syn-vilangin complex. This decreased deviation implies that by preventing excessive conformational drift, phenyl-vilangin improves the structural stability of α-syn fibrils. On the other hand, the somewhat higher RMSD values for the α-syn-vilangin complex indicates greater conformational flexibility, although overall structural integrity is not compromised. These findings support the molecular docking results, showing that phenyl-vilangin maintains stable connections in dynamic physiological conditions in addition to binding favourably in static docking.

RMSF Analysis

RMSF analysis was carried out to evaluate residue-level flexibility and to pinpoint areas of increased mobility within α-syn fibrils during ligand binding. Amyloid fibrils are naturally rigid, so both ligand-bound complexes show low RMSF values throughout the core β-sheet regions. Given that there are structural limitations, fluctuations are higher mostly in terminal and solvent-exposed areas. Crucially, the RMSF patterns of both complexes are quite similar, suggesting that neither ligand destabilises the α-syn fibril core. However, in a number of areas close to the binding pocket, the α-syn-phenyl-vilangin complex shows somewhat smaller variations in the RMSF, indicating localised stabilisation effects.

Table 1: The interaction energy between the three ligands and different sites of the α-synuclein fibril.

Site	Ligand	ΔG (kcal/mol)
Site 2	Vilangin	-6.7
	Phenyl-vilangin	-3.8
	Methyl-vilangin	-1.9
Site 3/13	Vilangin	-6.2
	Phenyl-vilangin	-7.9
	Methyl-vilangin	-3.6
Site 9	Vilangin	-2.7
	Phenyl-vilangin	-0.7
	Methyl-vilangin	0.5

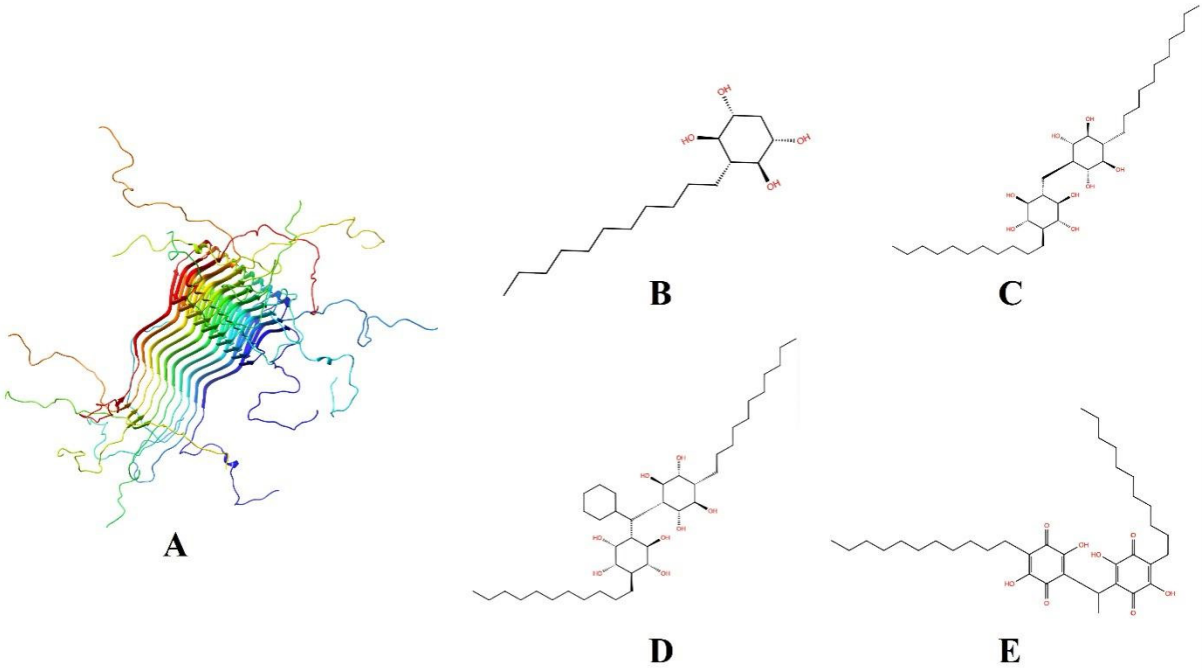

Figure 1: (A) The Three-Dimensional (3D) structure for α-synuclein (PDB ID: 2N0A). (B) The Two-Dimensional (2D) structure of embelin (the reference compound). (C) The 2D structure of vilangin. (D) The 2D structure of phenyl vilangin. (E) The 2D structure of methyl vilangin.

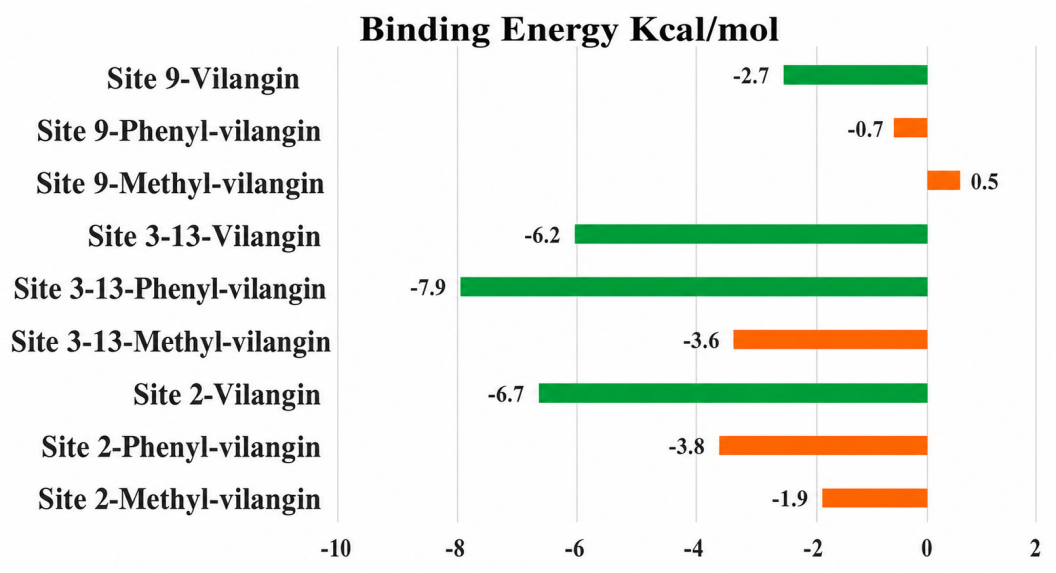

Figure 2a: The PDBePISA server was used to calculate the binding energies for the three ligands at each of the three sites on the α-synuclein fibril.

PCA and Essential Dynamics

PCA was applied to the MD trajectories to evaluate large-scale collective motions and crucial dynamics of the protein-ligand systems. For comparative analysis, the first two Principal Components (PC1 and PC2), which explain most of the motion variation, were employed. The α-syn-phenyl-vilangin complex shows a more constrained conformational space, suggesting limited large-scale motions and a preference for stable structural states. In contrast, the α-syn-vilangin complex presents a wider conformational range, indicating more flexibility and dynamic adaptation. Cosine content analysis confirmed the trustworthiness of the PCA results, demonstrating that the principal components represent significant collective motions rather than random diffusion.

FEL Analysis

The FELs created from PC1 and PC2 afford a thermodynamic view of the conformational stability of the complexes (Figure 4). The α-syn-phenyl-vilangin complex mostly occupies a single, energetically favourable structural state, as evidenced by the dominant, well-defined low-energy basin (Figure 4A). Strong and enduring protein-ligand interactions that stabilise the fibril architecture are reflected in this small basin. On the other hand, the α-syn-vilangin complex has various shallow energy minima, indicating the existence of multiple metastable conformations (Figure 4B). Despite the fact that these states are energetically feasible, their dispersion shows more conformational heterogeneity than the α-syn-phenyl-vilangin complex. Therefore, the FEL analysis shows that phenyl-vilangin more successfully limits α-syn to a stable energy minimum, improving overall complex stability and supporting the RMSD, RMSF, and PCA findings.

DISCUSSION

The current *in silico* study demonstrates the potential of benzoquinone derivatives as α-syn fibril stability modulators in PD. Phenyl-vilangin demonstrated the highest binding affinity at Site 3/13 among the evaluated drugs, indicating favorable interactions with a functionally significant area of the α-synuclein fibril. Additional hydrophobic and aromatic groups that improve protein-ligand interactions may be responsible for the better docking performance. The docking results were validated by MD simulations, which showed that the α-syn-phenyl-vilangin combination had better structural stability, less flexibility, and limited conformational motions in comparison to other complexes. A stable and energetically advantageous structural state was shown by PCA and FEL studies, indicating that phenyl-vilangin may successfully disrupt fibril dynamics and possibly prevent α-synuclein aggregation. All things considered, these results show that phenyl-vilangin is a viable lead chemical for additional experimental validation in the development of PD treatments.

Molecular docking and simulation studies reveal potential sites of interaction between α-syn and antioxidant compounds from *Camellia sp.* Theaflavin-3-3-digallate can reduce the α-syn structure's alpha-sheet structure to a loop region and shows the best interactions at -7.1 kcal/mol (Vats *et al.*, 2022). The effects of Curcumin (CUR) and Rosmarinic Acid (RA) on breaking the oligomer structure of PDB: 2N0A were investigated. To concentrate on the NAC region, they eliminated all N-terminal (N-ter) and C-terminal (C-ter) residues from their study (Rezaei Kamelabad *et al.*, 2021). The molecule DHF-BAHPC (8q) showed the greatest molecular docking score (-16.3120 kcal/mol) among the 40 DHF (7,8-Dihydroxyflavone) derived complexes, indicating a significant binding towards α-syn. The

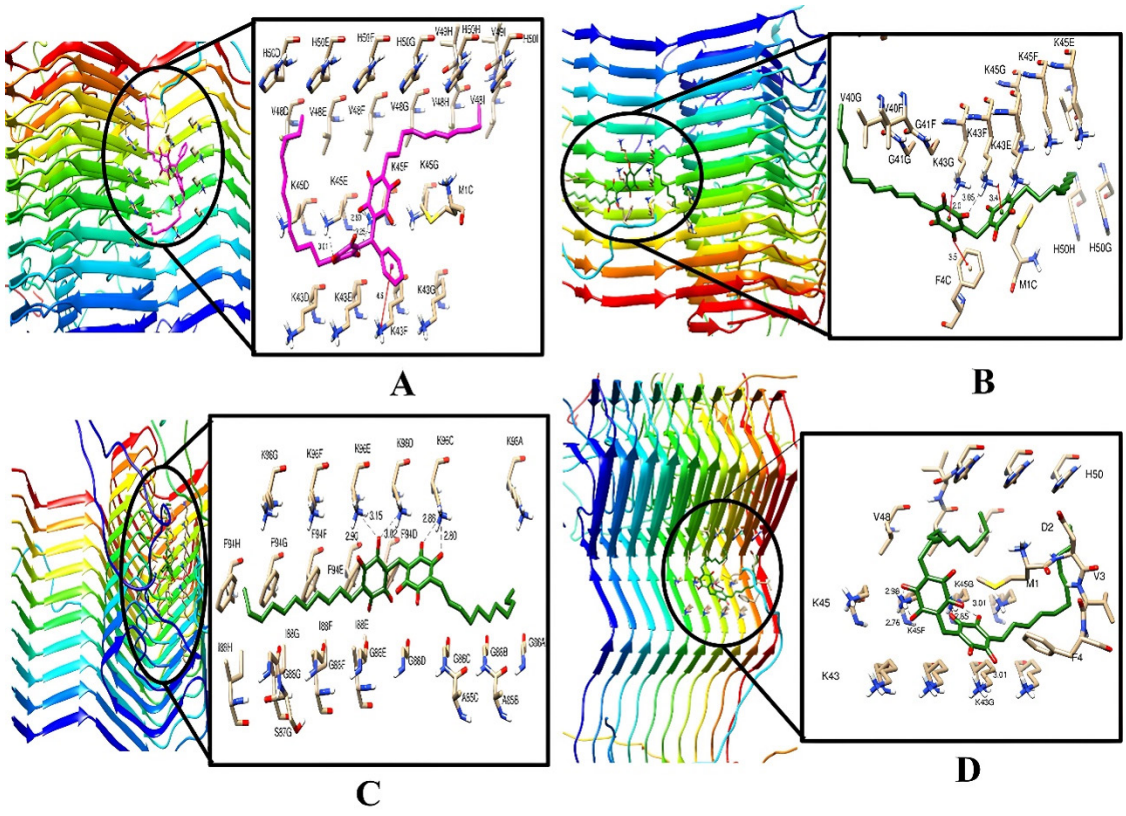

Figure 2b: The molecular interactions between vilangin, phenyl-vilangin, and methyl-vilangin towards the α-synuclein fibril. (A) Interactions between phenyl-vilangin and Site 3/13 of the α-synuclein fibril. (B) Interactions between vilangin and Site 2 of the α-synuclein fibril. (C) Interactions between vilangin and Site 9 of the α-synuclein fibril. (D) Interactions between vilangin and Site 3/13 of the α-synuclein fibril.

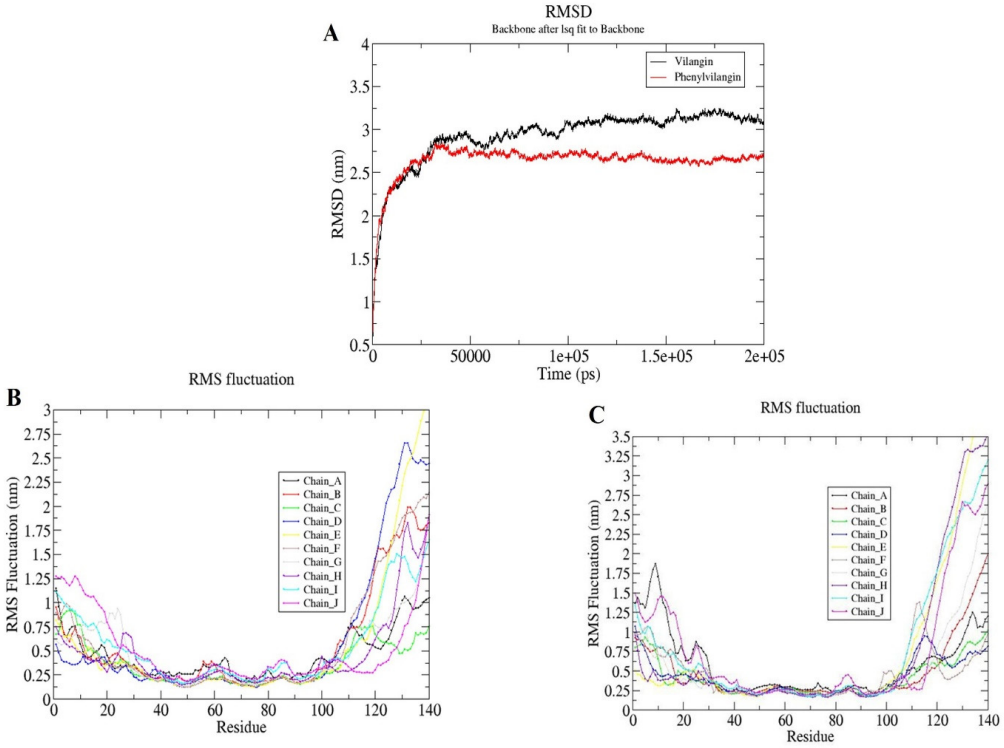

Figure 3: (A) The Root Mean Square Deviation (RMSD) of vilangin and phenyl-vilangin interactions with the α-synuclein fibril. The Root Mean Square (RMS) fluctuation of α-synuclein fibril chains considering (B) the interactions between phenyl-vilangin and Site 3/13 and (C) the interactions between vilangin and Site 3/13.

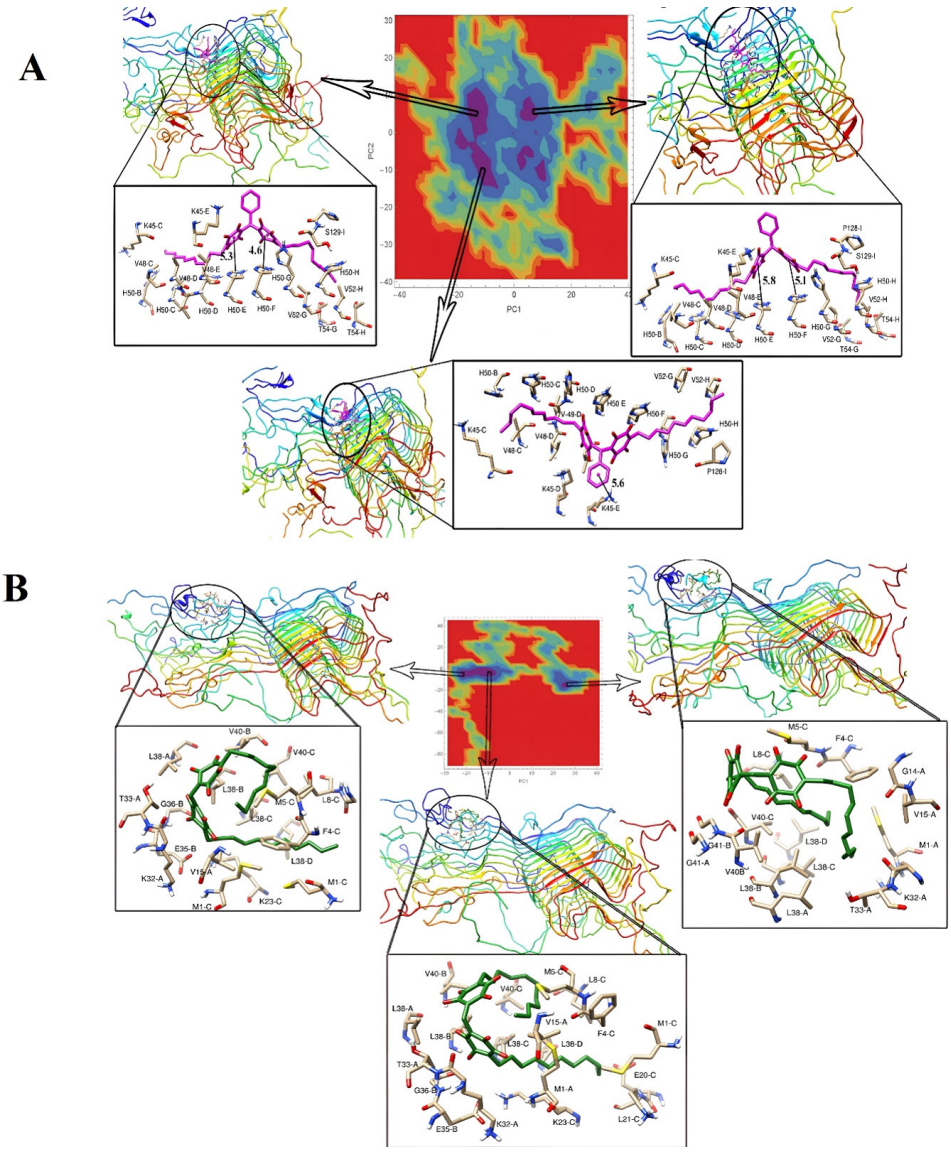

Figure 4: (A) Three representative structures are displayed from the most populated free energy minimum clusters along with the phenyl-vilangin interactions at Site 3/13 of the α-synuclein fibril. (B) Three representative structures are displayed from the most populated free energy minimum clusters along with the vilangin interactions at Site 3/13 of the α-synuclein fibril.

molecular dynamics simulation used to assess the stability of the ligand-protein complexes revealed that the ligands 8q, 8s, 8p, 8c, 8n, 8h, and DHF with α-syn complexes had little structural changes during the MD simulations. The binding mode study confirms that, with the exception of L-DOPA, DHF and its derivatives are building stable connections with the α-syn protein (Mohankumar *et al.*, 2020). The compound with PubChem ID 100968625 was chosen for additional study using the Molecular Dynamics (MD) simulation approach because it had the lowest free binding energy, ΔG0=-7.1 kcal.mol-1. MD trajectory analysis revealed that molecules of the chosen ligand (PubChem ID 1009686205) interact with the αSN trimer through an H-bond interaction, destabilizing the trimer's tight structure (Sahihi *et al.*, 2021). In this investigation Yu *et al.*, discovered that the Amento flavone was a relatively better ligand. According to these findings, amento flavone can bind to the active site of α-synuclein and stop the protein from self-associating, which could lead to the development of a Parkinson disease medication (Yu *et al.*, 2017) Siddiqui *et al.*, (2025) reported four new inhibitors (ZINC000150351590, ZINC000299817386, ZINC000085509805, and ZINC000095911811) with significant binding affinities (-9.43 to -9.06 kcal/mol) were found by screening the ZINC natural product library using a validated pharmacophore model. While MM/PBSA analysis revealed favorable binding free energies (-56.7 to -49.2 kcal/mol), molecular dynamics simulations verified stable protein-ligand complexes (average RMSD < 2.5 Å). Four naturally occurring inhibitors of α-syn aggregation have been identified as intriguing candidates for additional research in the drug discovery process for PD (Siddiqui *et al.*, 2025). Borah *et al.*, discovered that oleuropein aglycone interacted with α-synuclein's

N-terminal domain, preventing it from interacting with membranes and lipids to form cellular hazardous aggregates. The binding-free energy analysis revealed a significant binding affinity between α-synuclein and oleuropein aglycone (ΔGbind=-12.56 kcal mol-1 from MM-PBSA and ΔGbind=-27.41 kcal mol-1 from MM-GBSA). Thus, the results of this investigation support the impact of oleuropein aglycone on the structure and stabilization of α-synuclein monomer, which in turn promotes the formation of stable and nontoxic aggregates (Borah *et al.*, 2021).

The use of computational approaches to predict the interaction between benzoquinone derivatives and the α-syn fibril limits the current work. The docking investigation was performed using a single fibrillar α-syn structure (PDB ID: 2N0A), which may not fully capture the structural diversity and dynamic character of α-syn assemblies in physiological conditions. The biological components and cellular environment that influence α-syn aggregation cannot be accurately replicated by 200 ns MD simulations, despite the fact that they provide insight into complex stability and conformational behavior. Furthermore, to validate the anticipated binding affinities and stabilizing interactions, biochemical, cellular, and *in vivo* investigations are required. Therefore, more investigation is needed to ascertain the mechanism of action and therapeutic efficiency of phenyl-vilangin as a potential modulator of α-syn aggregation.

Integrated Interpretation and Lead Compound Identification

Based on integration of the molecular docking results, long-timescale MD simulations, and sophisticated trajectory analysis, phenyl-vilangin represents the most promising lead compound of the three analysed in the present study. Phenyl-vilangin shows the highest binding affinity with the α-syn fibril, and the complex presents better dynamic stability, less conformational variations, and a clearly characterised low-energy conformational landscape. Hence, phenyl-vilangin could serve as a stabilising drug that prevents α-syn aggregation. Vilangin also shows favourable binding to α-syn. Indeed, the α-syn-vilangin complex shows good stability, especially at Sites 2 and 3/13, but the complex is marginally less stable than the α-syn-phenyl-vilangin complex. It could be a useful scaffold or secondary option for additional optimisation. Methyl-vilangin, on the other hand, is unsuitable for further investigation due to relativity poor affinity for α-syn. Overall, this *in silico* study supports the potential of phenyl-vilangin in the development of treatment techniques targeting α-syn aggregation in PD and identifies it as a strong candidate for downstream experimental validation.

CONCLUSION

In this work, we evaluated the embelin-derived benzoquinone analogues vilangin, phenyl-vilangin, and methyl-vilangin against the α-syn fibril, a crucial target in Parkinson's disease, using an *in silico* approach that combined molecular docking, MD simulations, and essential dynamics analysis. The most promising compound is phenyl-vilangin, which shows excellent binding affinity, structural stability, and little conformational fluctuation, making it an ideal scaffold for controlling α-syn aggregation. While methyl-vilangin shows modest binding interactions, vilangin also demonstrates favourable characteristics, albeit with somewhat less stability compared with phenyl-vilangin. These results emphasise the potential of phenyl-vilangin in the development of therapeutic strategies against PD. Therefore, compounds that target α-syn aggregation in PD may be a crucial and strong lead drug for further experimental validation. Confirming the translational prospective of these drugs in therapeutic applications requires additional experimental validation, such as biophysical measures and aggregation inhibition experiments.

ACKNOWLEDGEMENT

We thank Dr. Matthew D Howell for critical reviewing of manuscript, technical inputs and manuscript editing, Biomedical Editor, St. Petersburg, FL, USA.

ABBREVIATIONS

α-syn: α-Synuclein; **CNS:** Central Nervous System; **FEL:** Free Energy Landscape; **LBs:** Lewy Bodies; **MD:** Molecular Dynamics; **NAC:** Non-Amyloid-β Component; **PCA:** Principal Component Analysis; **PD:** Parkinson's Disease; **PDB:** Protein Data Bank; **RMSD:** Root Mean Square Deviation; **RMSF:** Root Mean Square Fluctuation; **SNpc:** Substantia Nigra Pars Compacta.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

This work was supported by the award of Junior Research Fellowship to Nivetha Rajendiran by Saveetha Institute of Medical and Technical Sciences, Chennai - 602105.

AUTHORS CONTRIBUTION

NR: Performed the *in silico* studies (molecular docking and MD simulations) and wrote and revised the manuscript. KM: Performed the *in silico* studies (molecular docking and MD simulations), analysed the results, and revised the manuscript. GM: Analysed the *in silico* results and revised the manuscript. ES: Conceptualised the study and revised the manuscript. SS: Conceptualised and designed the study, supervised the work, and revised the manuscript. All authors have read and approved the final version of the manuscript.

SUMMARY

Molecular docking and dyamics simulations showed that phenyl-vilangin had the highest binding affinity for α-syn fibrils, particularly at Site 3/13. Additionally, because of phenyl-Vilangin's advantageous hydrophobic and aromatic interactions, it demonstrated increased stability. Plain vilangin also showed potential binding affinity, while methyl-Vilangin showed weaker interactions. MD analyses (RMSD, RMSF, PCA, and FEL) confirmed that phenyl-vilangin provides greater structural stability than vilangin and restricts the conformational flexibility of α-syn. Overall, phenyl-vilangin was shown to be the most promising alternative for stabilizing α-syn fibrils.

REFERENCES

Adam, H., Gopinath, S. C. B., Krishnan, H., Adam, T., Mohammed, M., *et al.* (2024). Cyclic and differential pulse voltammetric measurements on fibrils formation of alpha synuclein in Parkinson's disease by a gold interdigitated tetraelectrodes. Process Biochemistry, 136, 212-220. https://doi.org/https://doi.org/10.1016/j.procbio.2023.11.019

Alimohammadi, E., Nikzad, A., Khedri, M., Shafiee, S., Miri Jahromi, A., *et al.* (2021). Molecular Tuning of the Nano-Bio Interface: Alpha-Synuclein's Surface Targeting with Doped Carbon Nanostructures. ACS Appl Bio Mater, 4(8), 6073-6083. https://doi.org/10.1021/acsabm.1c00421

Borah, P., Sanjeev, A., & Mattaparthi, V. S. K. (2021). Computational investigation on the effect of Oleuropein aglycone on the α-synuclein aggregation. Journal of Biomolecular Structure and Dynamics, 39(4), 1259-1270. https://doi.org/10.1080/07391102.2020.1728384

De Sancho, D. (2022). Phase separation in amino acid mixtures is governed by composition. bioRxiv, 121(21), 4119-4127. 2022.2003.2002.482633. https://doi.org/10.1101/2022.03.02.482633

Elkouzi, A., Vedam-Mai, V., Eisinger, R. S., & Okun, M. S. (2019). Emerging therapies in Parkinson disease - repurposed drugs and new approaches. Nat Rev Neurol, 15(4), 204-223. https://doi.org/10.1038/s41582-019-0155-7

Endo, H., Ono, M., Takado, Y., Matsuoka, K., Takahashi, M., *et al.* (2024). Imaging α-synuclein pathologies in animal models and patients with Parkinson's and related diseases. Neuron, 112(15), 2540-2557.e2548. https://doi.org/https://doi.org/10.1016/j.neuron.2024.05.006

Kouli, A., Torsney, K. M., & Kuan, W. L. (2018). Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis. In T. B. Stoker & J. C. Greenland (Eds.), Parkinson's Disease: Pathogenesis and Clinical Aspects. Codon Publications

Copyright: The Authors. https://doi.org/10.15586/codonpublications.parkinsonsdisease.2018.ch1

Lang, A. E., & Espay, A. J. (2018). Disease Modification in Parkinson's Disease: Current Approaches, Challenges, and Future Considerations. Mov Disord, 33(5), 660-677. https://doi.org/10.1002/mds.27360

Maisuradze, G. G., & Leitner, D. M. (2007). Free energy landscape of a biomolecule in dihedral principal component space: sampling convergence and correspondence between structures and minima. Proteins, 67(3), 569-578. https://doi.org/10.1002/prot.21344

Martonák, R., Laio, A., & Parrinello, M. (2003). Predicting crystal structures: the Parrinello-Rahman method revisited. Phys Rev Lett, 90(7), 075503. https://doi.org/10.1103/PhysRevLett.90.075503

Mohankumar, T., Chandramohan, V., Lalithamba, H. S., Jayaraj, R. L., Kumaradhas, P., *et al.* (2020). Design and Molecular dynamic Investigations of 7,8-Dihydroxyflavone Derivatives as Potential Neuroprotective Agents Against Alpha-synuclein. Scientific Reports, 10(1), 599. https://doi.org/10.1038/s41598-020-57417-9

Negi, S., Khurana, N., & Duggal, N. (2024). The misfolding mystery: α-synuclein and the pathogenesis of Parkinson's disease. Neurochemistry International, 177, 105760. https://doi.org/https://doi.org/10.1016/j.neuint.2024.105760

Nieto-Giraldo, D. F., Rodríguez, J. M. R., & Torres-Osorio, J. (2026). Analysis of the Effect of the Magnetic Field on Water Flux Through TIP3;1 Aquaporins Using Molecular Dynamics in GROMACS. The Journal of Membrane Biology, 259(1), 7. https://doi.org/10.1007/s00232-025-00368-x

Papaleo, E., Mereghetti, P., Fantucci, P., Grandori, R., & De Gioia, L. (2009). Free-energy landscape, principal component analysis, and structural clustering to identify representative conformations from molecular dynamics simulations: the myoglobin case. J Mol Graph Model, 27(8), 889-899. https://doi.org/10.1016/j.jmgm.2009.01.006

Poewe, W., Seppi, K., Tanner, C. M., Halliday, G. M., Brundin, P., *et al.* (2017). Parkinson disease. Nat Rev Dis Primers, 3(1), 17013. https://doi.org/10.1038/nrdp.2017.13

Rajendiran, N., Sivanesan, S., Rajkumar, E., Sugumar, V., Narayanaswamy, R., *et al.* (2026). Evaluating the Curative Potential of Vilangin for Parkinson's Disease Treatment through *in vitro* and *in silico* Approach. Pharmacogn Res, 18(3), 843-854. https://doi.org/10.5530/pres.20260225

Ramachandra, V. H., Sivanesan, S., Koppal, A., Anandakumar, S., Howell, M. D., *et al.* (2022). Embelin and levodopa combination therapy for improved Parkinson's disease treatment. Transl Neurosci, 13(1), 145-162. https://doi.org/10.1515/tnsci-2022-0224

Rao, S. P., Sharma, N., & Kalivendi, S. V. (2020). Embelin averts MPTP-induced dysfunction in mitochondrial bioenergetics and biogenesis via activation of SIRT1. Biochim Biophys Acta Bioenerg, 1861(3), 148157. https://doi.org/10.1016/j.bbabio.2020.148157

Rezaei Kamelabad, M., Jahanbin Sardroodi, J., Rastkar Ebrahimzadeh, A., & Ajamgard, M. (2021). Influence of curcumin and rosmarinic acid on disrupting the general properties of Alpha-Synuclein oligomer: Molecular dynamics simulation. J Mol Graph Model, 107, 107963. https://doi.org/10.1016/j.jmgm.2021.107963

Sahihi, M., Gaci, F., & Navizet, I. (2021). Identification of new alpha-synuclein fibrillogenesis inhibitor using *in silico* structure-based virtual screening. Journal of Molecular Graphics and Modelling, 108, 108010. https://doi.org/https://doi.org/10.1016/j.jmgm.2021.108010

Samantaray, M., Sahoo, S., Sahoo, D. P., Sethi, G., Singh, S., *et al.* (2025). Computational identification of dual COX-1 and NIK inhibitors from marine microalga *Chlorella vulgaris*. Journal of Genetic Engineering and Biotechnology, 23(3), 100531. https://doi.org/https://doi.org/10.1016/j.jgeb.2025.100531

Sardar Sinha, M., Villamil Giraldo, A. M., Öllinger, K., Hallbeck, M., & Civitelli, L. (2018). Lipid vesicles affect the aggregation of 4-hydroxy-2-nonenal-modified α-synuclein oligomers. Biochim Biophys Acta Mol Basis Dis, 1864(9 Pt B), 3060-3068. https://doi.org/10.1016/j.bbadis.2018.06.020

Siddiqui, A. J., Jahan, S., Saxena, J., Sachidanandan, M., Badraoui, R., & Adnan, M. (2025). Targeting the alpha-synuclein protein to treat Parkinson's disease using novel inhibitors identified using an integrated computational drug development approach. *In silico* Pharmacology, 13(3), 168. https://doi.org/10.1007/s40203-025-00477-4

Thangavelu, L., Moglad, E., Afzal, M., Almalki, W. H., Malathi, H., *et al.* (2024). Non-coding RNAs in Parkinson's disease: Regulating SNCA and alpha-synuclein aggregation. Pathology - Research and Practice, 261, 155511. https://doi.org/https://doi.org/10.1016/j.prp.2024.155511

Vats, S., Kondabala, R., & Saxena, S. (2022). Identification of alpha-Synuclein Disaggregator from *Camellia* sp. Insight of Molecular Docking and Molecular Dynamics Simulations. ChemistrySelect, 7(10), e202104131. https://doi.org/https://doi.org/10.1002/slct.202104131

Vidović, M., & Rikalovic, M. G. (2022). Alpha-Synuclein Aggregation Pathway in Parkinson's Disease: Current Status and Novel Therapeutic Approaches. Cells, 11(11), 1732. https://doi.org/10.3390/cells11111732

Wardhan, Y., Vishwas, S., Porselvi, A., Singh, S. K., & Kakoty, V. (2024). Exploring the complex interplay between Parkinson's disease and BAG proteins. Behavioural Brain Research, 469, 115054. https://doi.org/https://doi.org/10.1016/j.bbr.2024.115054

Yu, S., Yan, H., Zhang, L., Shan, M., Chen, P., *et al.*(2017). A Review on the Phytochemistry, Pharmacology, and Pharmacokinetics of Amentoflavone, a Naturally-Occurring Biflavonoid. Molecules, 22(2), 299. https://doi.org/10.3390/molecules22020299

Cite this article: Rajendiran N, Muthu K, Manivel G, Sukumar E, Sivanesan S. Identification of Potential Plant-Based Bioactive Compounds as α-Synuclein Targets via Molecular Docking and Molecular Dynamics Simulations. Pharmacog Res. 2027;19(1):329-37.