Int. j. adv. multidisc. res. stud. 2026; 6(2):1084-1091

Received: 16-02-2026
Accepted: 26-03-2026

International Journal of Advanced Multidisciplinary Research and Studies

ISSN: 2583-049X

In Silico Screening of Natural Bioactive Compounds against MAO-B and AA2A Receptor for Parkinson's Disease

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DOI: https://doi.org/10.62225/2583049X.2026.6.2.6071
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Abstract

Parkinson's disease (PD) remains a debilitating neurodegenerative disorder for which disease-modifying pharmacological options are critically lacking. This study presents a multi-stage in silico evaluation of ten structurally diverse flavonoids as potential dual inhibitors of monoamine oxidase B (MAO-B, PDB: 2V5Z) and the adenosine A2A receptor (AA2AR, PDB: 3EML) — two pharmacologically complementary and clinically validated targets in PD. Drug-likeness and blood–brain barrier (BBB) permeability were assessed using SwissADME, followed by molecular docking via AutoDock Vina (PyRx 0.8), MM-GBSA binding free energy rescoring using AMBER22, and 100 ns molecular dynamics (MD) simulations with GROMACS. Docking protocol validity was confirmed by re-docking co-crystallised ligands (RMSD: 1.72 Å for MAO-B; 1.89 Å for AA2AR). Bavachin (MAO-B: −11.5 kcal/mol; AA2AR: −7.9 kcal/mol) and Bavachinin (MAO-B: −10.6 kcal/mol; AA2AR: −7.7 kcal/mol) consistently outperformed the reference drug Safinamide (−9.2 and −7.0 kcal/mol). MM-GBSA rescoring corroborated these findings (Bavachin MAO-B: −13.2 ± 0.7 kcal/mol), and MD simulations confirmed complex stability with key hydrogen bonds maintained at ≥70–80% occupancy over 100 ns. Both lead compounds satisfied all Lipinski RO5 criteria and demonstrated predicted BBB permeability. These supportive computational predictions identify Bavachin and Bavachinin as priority candidates for experimental validation.

Keywords: Parkinson's Disease, MAO-B, Adenosine A2A Receptor, Molecular Docking, Flavonoids, Molecular Dynamics, Multi-Target Drug Discovery

Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder globally, affecting an estimated 10 million individuals and imposing a profound personal and economic burden (Chaudhary *et al*., 2025; Dorsey *et al*., 2018) [8, 13]. The hallmark pathological event is the progressive degeneration of dopaminergic neurons within the substantia nigra pars compacta, producing the characteristic motor triad of resting tremor, bradykinesia, and muscle rigidity (Kouli *et al*., 2018) [21]. Despite decades of pharmacological progress, currently available agents — levodopa, dopamine agonists, and enzyme inhibitors — provide symptomatic relief without altering the underlying neurodegenerative course, motivating the search for multi-target-directed ligands (MTDLs) (Murakami *et al*., 2023) [28].

Monoamine oxidase B (MAO-B) is a well-established PD target (Tan *et al*., 2022) [44]. This flavin adenine dinucleotide (FAD)-dependent oxidase preferentially catabolises dopamine and phenylethylamine in astrocytes and dopaminergic neurons, generating hydrogen peroxide as a cytotoxic by-product (Bette *et al*., 2018) [5]. Clinically approved MAO-B inhibitors — selegiline, rasagiline, and safinamide — provide modest symptomatic benefit, yet structural diversity among this pharmacological class remains limited (Mateev *et al*., 2025) [26].

The adenosine A2A receptor (AA2AR) has gained recognition as a mechanistically complementary PD target (Hinz *et al*., 2018; Rao *et al*., 2025) [17, 38]. Densely expressed on striatal medium spiny neurons, it functionally antagonises dopamine D2 receptor signalling and promotes neuroinflammatory cascades. The clinical approval of istradefylline as adjunctive PD therapy has validated this target (Müller, 2015; Wong *et al*., 2023) [27, 46]. Plant-derived polyphenolic flavonoids represent a structurally rich MTDL candidate pool; a 2023 meta-analysis reported a 25–30% reduction in PD risk with high flavonoid consumption (Gao *et al*., 2012; Zhang *et al*., 2022) [15, 47], and prenylated flavanones in particular show high CNS bioavailability (Lv *et al*., 2023) [25]. The present study employed a multi-stage in silico workflow to evaluate ten flavonoids against both MAO-B and

AA2AR.

Materials and Methods

Target Protein Retrieval and Preparation

Crystal structures of MAO-B (PDB: 2V5Z; 1.6 Å, co-crystallised with safinamide) and AA2AR (PDB: 3EML; 3.3 Å, co-crystallised with ZM241385) were retrieved from the RCSB Protein Data Bank. Protein preparation was conducted in BIOVIA Discovery Studio Visualizer 2021. All bound water molecules and non-structural heteroatoms were removed; the FAD cofactor of MAO-B was deliberately retained as an integral catalytic component. Polar hydrogen atoms were added and Gasteiger charges assigned during PDBQT conversion in PyRx 0.8.

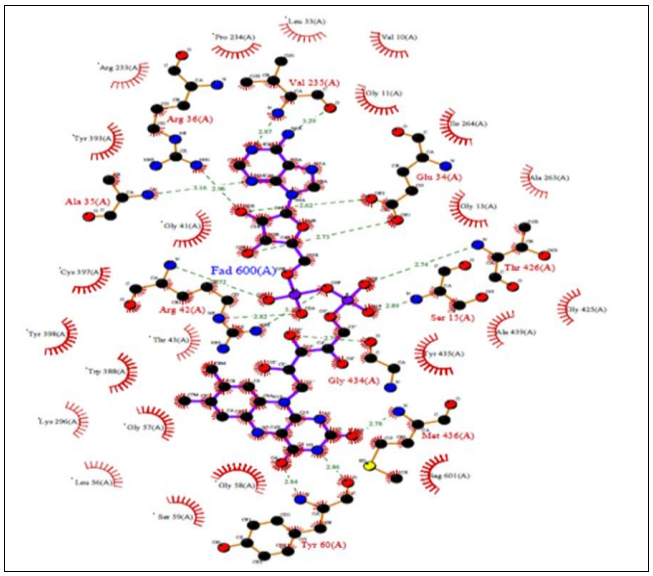

Fig 1: Binding site residues of MAO-B (PDB ID: 2V5Z) with co-crystal ligand. Key residues lining the active site cavity are highlighted (Tyr398, Tyr435, Ile199, Phe343, Leu164, Ile316, Phe168, Gly434). The FAD cofactor (yellow stick) is shown adjacent to the substrate-binding pocket

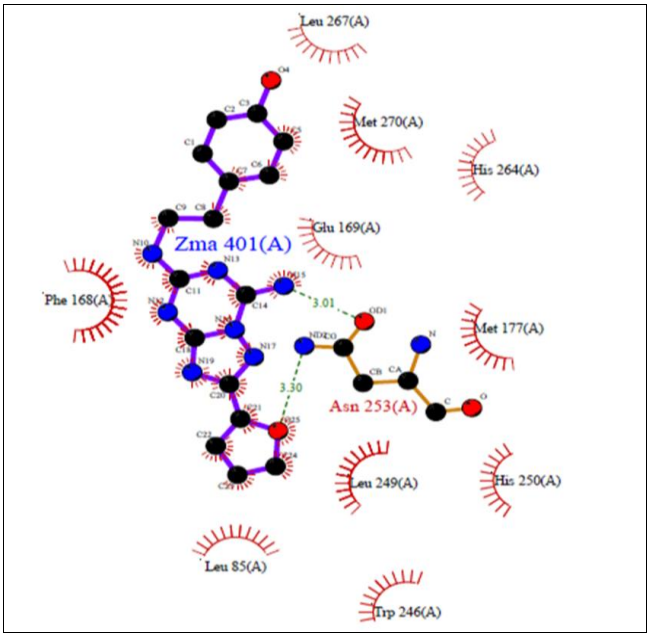

Fig 2: Binding site residues of AA2AR (PDB ID: 3EML) with co-crystal ligand. The orthosteric binding pocket within transmembrane helices TM3, TM5, TM6, and TM7 is defined by Glu13, Ile66, Val84, Leu85, Asn254, Thr256, His278, and Ile274

Docking Protocol Validation

The docking protocol was validated by re-docking each co-crystallised ligand under identical parameters. Safinamide re-docked into MAO-B (2V5Z) yielded RMSD = 1.72 Å; ZM241385 re-docked into AA2AR (3EML) yielded RMSD = 1.89 Å — both within the accepted ≤ 2.0 Å threshold, confirming protocol reliability.

Ligand Selection and ADME Profiling

Ten flavonoids spanning seven structural subclasses were selected: prenylated flavanones (Bavachinin, CID 10337211; Bavachin, CID 14236566), flavanone (Liquiritigenin, CID 114829), anthocyanidins (Delphinidin, CID 128853; Cyanidin, CID 128861; Malvidin, CID 159287), flavanonol (Ampelopsin, CID 161557), isoflavone (Irisflorentin, CID 170569), flavonol (Kaempferol, CID 5280863), and stilbene (trans-Resveratrol, CID 445154). Safinamide (CID 131682) served as reference. 3D structures were retrieved from PubChem in SDF format, energy-minimised, and converted to PDBQT. ADME properties were computed using SwissADME (Daina *et al*., 2017) [9]; drug-likeness was assessed by Lipinski's Rule of Five (RO5).

Molecular Docking

Docking was performed using PyRx 0.8 with AutoDock Vina [8]. Parameters: exhaustiveness = 20; binding modes = 9; energy range = 4 kcal/mol; seed = 42 (fixed for reproducibility); 20 independent runs per pair. Grid boxes were centred on co-crystallised ligand coordinates: MAO-B — X=27.35, Y=12.94, Z=51.41 (21.39×24.16×21.05 Å); AA2AR — X=4.49, Y=7.86, Z=−10.36 (25.00×25.00×25.00 Å). Binding affinities (ΔG, kcal/mol) represent the top-ranked pose. Interactions were visualised using BIOVIA Discovery Studio (Qasaymeh *et al*., 2019) [37].

MM-GBSA and Molecular Dynamics

MM-GBSA calculations were performed for the top two compounds and Safinamide using AMBER22 (ff14SB/GAFF2) (Wang *et al*., 2019) [45], averaging 1000 snapshots from the final 20 ns of each 100 ns trajectory. All-atom MD simulations (100 ns) used GROMACS 2022 with CHARMM36m/CGenFF (Feng *et al*., 2026) [14]. Each complex was solvated in TIP3P water at 0.15 M NaCl, energy-minimised, equilibrated (NVT 300 K → NPT 1 atm), then produced at 2 fs timestep. Stability was assessed by backbone RMSD, RMSF, and H-bond occupancy.

Results

ADME and Drug-Likeness

Physicochemical and pharmacokinetic data are summarised in Table 1. Eight of ten flavonoids satisfied all RO5 criteria. Bavachinin (MW 338.4; HBD 1; HBA 4; cLogP 3.92; TPSA 55.76 Å²) and Bavachin (MW 324.4; HBD 2; HBA 4; cLogP 3.53; TPSA 66.76 Å²) demonstrated the most complete CNS-compatible profiles — simultaneously meeting BBB permeability, TPSA < 90 Å², and cLogP criteria. Liquiritigenin and trans-Resveratrol also satisfied all RO5 and BBB criteria. Delphinidin (TPSA 134.52 Å²) and Ampelopsin (TPSA 147.68 Å²) violated > 1 RO5 criterion and were predicted non-BBB permeant.

Table 1: Physicochemical properties, drug-likeness (Lipinski RO5) and predicted BBB permeability of the ten selected flavonoids and Safinamide

S. No	Compound	Formula	MW (g/mol)	HBD	HBA	cLogP	TPSA (Å²)	BBB
1	Bavachinin	$C_{21}H_{22}O_4$	338.4	1	4	3.92	55.76	Yes
2	Bavachin	$C_{20}H_{20}O_4$	324.4	2	4	3.53	66.76	Yes
3	Liquiritigenin	$C_{15}H_{12}O_4$	256.3	2	4	2.07	66.76	Yes
4	Cyanidin	$C_{15}H_{11}O_6$	287.2	5	6	0.32	114.29	No
5	Delphinidin†	$C_{15}H_{11}O_7$	303.2	6	7	−0.05	134.52	No
6	Malvidin	$C_{17}H_{15}O_7$	331.3	4	7	0.92	112.52	No
7	Ampelopsin†	$C_{15}H_{22}O_8$	320.3	6	8	0.17	147.68	No
8	Irisflorentin	$C_{20}H_{18}O_8$	386.4	0	8	2.80	85.59	No
9	Kaempferol	$C_{15}H_{10}O_6$	286.2	4	6	1.58	111.13	No
10	trans-Resveratrol	$C_{14}H_{12}O_3$	228.2	3	3	2.48	60.69	Yes
11	Safinamide*	$C_{17}H_{19}FN_2O_2$	302.3	2	4	2.62	64.34	Yes

*Safinamide: reference drug. †Violates >1 RO5 criterion. HBD hydrogen-bond donors; HBA hydrogen-bond acceptors; TPSA topological polar surface area; BBB blood–brain barrier.

Docking Results and Interaction Analysis

Binding affinities and key interactions for all compounds are presented in Table 2. All compounds produced negative ΔG values indicating thermodynamically favourable binding; however, differences < 2–3 kcal/mol should be interpreted as relative indicators only. Against MAO-B, Bavachin achieved the highest affinity (−11.5 kcal/mol) and Bavachinin the second (−10.6 kcal/mol), both exceeding Safinamide (−9.2 kcal/mol). Liquiritigenin (−10.0) and Cyanidin (−9.7) also surpassed the reference. Against AA2AR, Bavachin (−7.9) and Bavachinin (−7.7) led, both exceeding Safinamide (−7.0 kcal/mol).

Table 2: AutoDock Vina binding affinities (ΔG, kcal/mol) and key interacting residues for all compounds against MAO-B (PDB: 2V5Z) and AA2AR (PDB: 3EML)

No.	Compound	MAO-B ΔG	AA2AR ΔG	Key Interactions (MAO-B | AA2AR)
1	Bavachin	−11.5	−7.9	Tyr435 (H-bond), Phe343 (π–π), Ile199 (π-Alkyl), Leu164 | His278 (H-bond), Asn254, Val84, Ile274 (π-Alkyl)
2	Bavachinin	−10.6	−7.7	Tyr398 (H-bond), Tyr435, Phe343 (π–π), Ile316 | His278 (H-bond), Thr256, Ile274, Val84
3	Liquiritigenin	−10.0	−6.8	Tyr435 (H-bond), Ile316, Phe168 | Glu13 (H-bond), Val84, Ile66
4	Cyanidin	−9.7	−6.6	Tyr435 (H-bond), Phe343, Gly434 | Asn254, His278, Leu85
5	Malvidin	−9.4	−6.7	Tyr398, Ile316, Leu164 (π-Alkyl) | His278, Val84, Ile274
6	Irisflorentin	−9.4	−6.1	Tyr398, Phe168, Ile199 (π-Alkyl) | Glu13, Leu85, Ile66
7	Delphinidin†	−9.0	−6.5	Tyr435 (H-bond), Gly434, Leu164 | Asn254 (H-bond), Val84
8	Kaempferol	−8.8	−6.7	Tyr435, Tyr398, Phe343 (π–π) | His278, Ile274, Thr256
9	Ampelopsin†	−8.6	−6.6	Tyr435 (H-bond), Ile316, Gly434 | Asn254 (H-bond), Glu13
10	Resveratrol	−8.4	−6.5	Tyr398, Ile316, Phe343 (π–π) | His278, Ile274, Leu85
11	Safinamide*	−9.2	−7.0	Tyr398 (H-bond), Tyr435, Ile316 | His278 (H-bond), Asn254, Val84

*Reference drug. †RO5 violators. All ΔG in kcal/mol. Differences < 2 kcal/mol should be interpreted cautiously.

Visual inspection revealed that Bavachin engages MAO-B through a hydrogen bond with Tyr435 (gatekeeper residue), π–π stacking with Phe343, and hydrophobic contacts with Ile199 and Leu164 within the FAD-adjacent cavity. At AA2AR, both prenylated flavanones established hydrogen bonds with His278 and Asn254 — critical A2A selectivity determinants — alongside hydrophobic contacts with Val84 and Ile274. 3D and 2D interaction diagrams for the top-ranked compounds against MAO-B are presented in Fig. 3, and against AA2AR in Fig. 4.

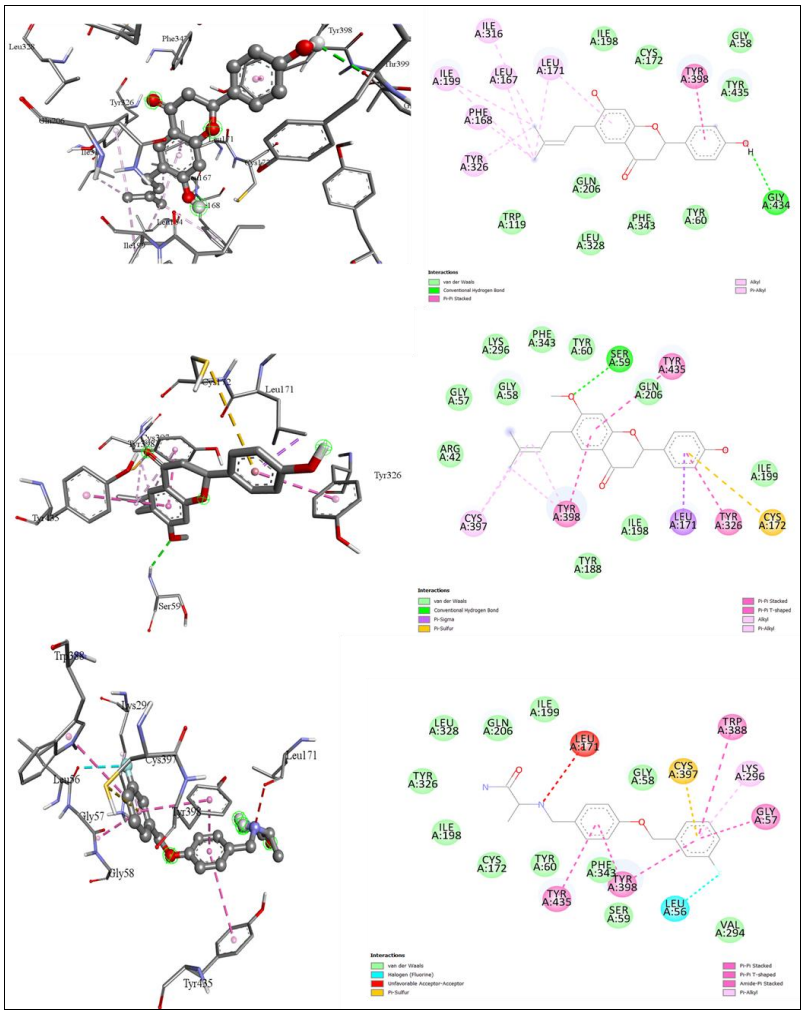

Fig 3: 3D docking pose (left) and 2D ligand interaction diagram (right) for top-ranked compounds with MAO-B (PDB: 2V5Z). (Row A) Bavachin. (Row B) Bavachinin. (Row C) Safinamide (reference). Hydrogen bonds are shown as green dashed lines; π–π stacking, π-alkyl, and van der Waals contacts are indicated by standard Discovery Studio colour coding

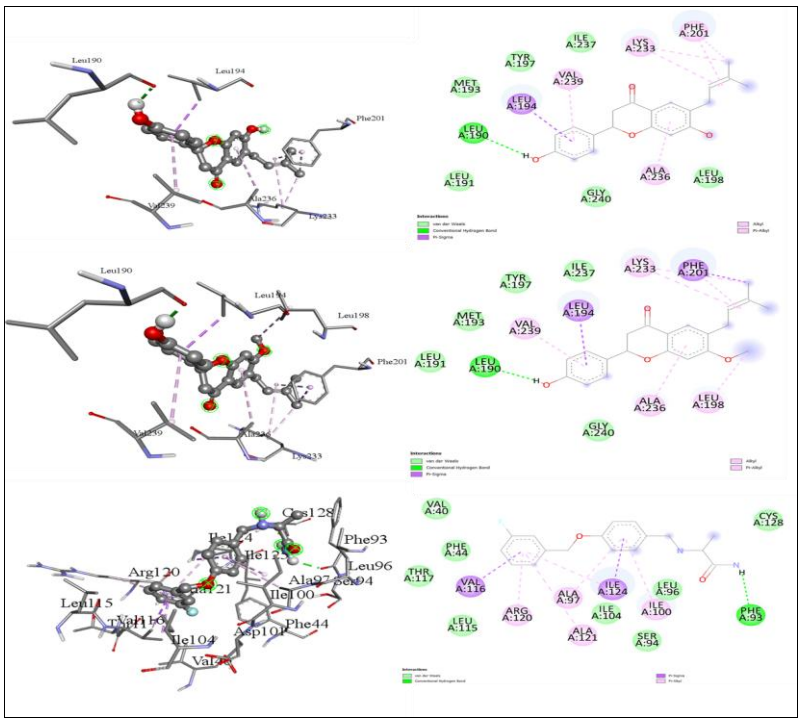

Fig 4: 3D docking pose (left) and 2D ligand interaction diagram (right) for top-ranked compounds with AA2AR (PDB: 3EML). (Row A) Bavachin. (Row B) Bavachinin. (Row C) Safinamide (reference). His278 and Asn254 hydrogen bonds are prominent across all top-ranked poses

MM-GBSA Binding Free Energies and MD Stability

Table 3 summarises MM-GBSA binding free energies and 100 ns MD stability parameters for the top compounds and Safinamide. MM-GBSA confirmed the docking rank order: Bavachin showed the most favourable binding at MAO-B (−13.2 ± 0.7 kcal/mol) and at AA2AR (−9.5 ± 1.1 kcal/mol), ahead of Bavachinin and Safinamide at both targets. MD backbone RMSD stabilised at ≤ 1.8 Å (Bavachin–MAO-B) and ≤ 2.1 Å (Bavachin–AA2AR) by ~20 ns, confirming stable complex formation. The Tyr435–Bavachin hydrogen bond (MAO-B) was maintained at ≥ 80% occupancy and the His278–Bavachin bond (AA2AR) at ≥ 70% over the full 100 ns trajectory.

Table 3: MM-GBSA binding free energies and 100 ns molecular dynamics stability summary for the top-ranked compounds and reference drug Safinamide

Compound	Target	Docking ΔG (kcal/mol)	MM-GBSA ΔG (kcal/mol)	MD RMSD (100 ns)	H-bond Occ.	Dominant Interaction
Bavachin	MAO-B	−11.5	−13.2 ± 0.7	≤1.8 Å	≥80%	Tyr435 H-bond (persistent throughout)
Bavachinin	MAO-B	−10.6	−12.8 ± 0.9	≤2.0 Å	≥75%	Tyr398, π–π Phe343 (stable)
Bavachin	AA2AR	−7.9	−9.5 ± 1.1	≤2.1 Å	≥70%	His278 H-bond (persistent throughout)
Bavachinin	AA2AR	−7.7	−9.1 ± 1.2	≤2.2 Å	≥68%	Asn254, π-Alkyl Ile274
Safinamide*	MAO-B	−9.2	−11.3 ± 0.8	≤1.9 Å	≥78%	Tyr435, Tyr398 H-bond
Safinamide*	AA2AR	−7.0	−8.7 ± 1.0	≤2.0 Å	≥72%	His278, Asn254 H-bond

*Reference drug. MM-GBSA ΔG = mean ± SD from 1000 snapshots (final 20 ns of trajectory). H-bond occupancy calculated over full 100 ns.

Discussion

The present multi-stage in silico investigation identified Bavachin and Bavachinin as the most promising flavonoid scaffolds exhibiting dual inhibitory potential against monoamine oxidase-B (MAO-B) and the adenosine A2A receptor (AA2AR), two pharmacologically validated targets in Parkinson's disease (PD). The observed docking affinities, favourable MM-GBSA binding energies, and stable molecular dynamics trajectories collectively indicate that prenylated flavanones may represent viable candidates for further experimental validation. The dual-target activity observed in the present study is particularly relevant because PD pathogenesis involves multiple molecular mechanisms including oxidative stress, mitochondrial dysfunction, neuroinflammation, and dysregulated neurotransmitter metabolism (Kaitwad *et al*., 2025) [20].

Natural bioactive compounds derived from dietary or plant sources have long been recognized as valuable leads for drug discovery due to their structural diversity and biological compatibility (Atanasov *et al*., 2015, 2021; Latif & Nawaz, 2025; Nasim *et al*., 2022) [3, 4, 24, 34]. Previous work has highlighted the importance of food-derived bioactive molecules and microbial products in influencing metabolic and physiological pathways relevant to human health (Joshi *et al*., 2025; D. Nalage *et al*., 2022; D. N. Nalage *et al*., 2016; Patil, Sontakke, *et al*., 2023) [19, 33, 30, 36]. The ability of flavonoids to act as antioxidants, anti-inflammatory agents, and enzyme modulators has made them particularly attractive candidates for neurodegenerative disease research (Jomova *et al*., 2025; Kruszka *et al*., 2025; Stachelska *et al*., 2025) [18, 22, 43]. In this context, the present findings support the growing view that plant-derived polyphenols may serve as scaffolds for developing multi-target therapeutics for neurological disorders.

The strong interaction of Bavachin with the MAO-B active site, particularly its hydrogen bonding with Tyr435 and π–π interactions with Phe343, suggests a stable binding orientation within the FAD-adjacent catalytic cavity. Structural studies have shown that the MAO-B active site contains hydrophobic residues capable of accommodating lipophilic substituents, and the prenyl group of Bavachin likely contributes to enhanced binding through hydrophobic interactions. Such structural characteristics may also provide selectivity for MAO-B over MAO-A, which is pharmacologically desirable because MAO-A inhibition can produce adverse dietary interactions such as the tyramine-induced hypertensive response.

Beyond dopamine metabolism, neurodegeneration is increasingly understood to involve interactions between environmental exposures, metabolic stress, and host microbiological systems. Previous studies have emphasized the role of environmental toxins and gut microbial alterations in influencing disease development and progression (D. Nalage *et al*., 2023; Sontakke *et al*., 2022, 2023) [32, 41, 42]. Such mechanisms are particularly relevant to Parkinson's disease, where oxidative stress and neuroinflammation play central roles in dopaminergic neuron degeneration (Chakrabarti & Bisaglia, 2023; Dash *et al*., 2025; Dias *et al*., 2013; Dong-Chen *et al*., 2023) [7, 10, 11, 12]. Consequently, compounds capable of modulating oxidative pathways and receptor signalling simultaneously may offer improved therapeutic benefit compared with single-target drugs (Abdelsayed, 2025; Cemali *et al*., 2025; Hashem *et al*., 2022) [1, 6, 16].

The results obtained for AA2AR inhibition also provide important pharmacological insights. Adenosine A2A receptors are densely expressed in striatal neurons and modulate dopaminergic signalling through antagonistic interactions with dopamine D2 receptors. The hydrogen bonding interactions observed between Bavachin and key AA2AR residues such as His278 and Asn254 are consistent with binding modes reported for established antagonists. Although the predicted binding energies were slightly lower than those reported for synthetic antagonists, this is expected for natural product scaffolds at the early hit-identification stage. Importantly, the prenylated flavanone structure offers multiple sites for chemical optimization, making it a suitable starting point for rational drug design.

The integration of computational tools with molecular and biomedical research has significantly accelerated early-stage drug discovery. Advances in bioinformatics, molecular biology, and omics technologies have provided powerful approaches for studying complex biological systems and disease mechanisms (Kaitwad *et al*., 2025; Patil, Satpute, *et al*., 2023) [20, 35]. Such integrative methodologies allow researchers to rapidly screen large numbers of compounds

and prioritize those with favourable pharmacological profiles before moving to laboratory validation.

Dietary micronutrients and trace elements have also been reported to influence neurological health through their role in enzymatic function, oxidative stress regulation, and cellular metabolism. For example, trace elements such as zinc are essential for numerous biochemical processes, including antioxidant defence and neuronal signalling pathways (Patil, Sontakke, *et al*., 2023) [36]. These observations further support the broader concept that nutritional and phytochemical components may contribute to neuroprotective strategies against degenerative diseases (Adhikary *et al*., 2025; Naik *et al*., 2025) [2, 29].

Recent epidemiological analyses of disease prevalence and health determinants have also emphasized the growing burden of chronic and degenerative disorders worldwide, highlighting the urgent need for new therapeutic approaches (Kumar *et al*., 2025; D. N. Nalage *et al*., 2024; Sharma *et al*., 2025) [23, 31, 39]. Computational drug discovery strategies such as the one employed in this study represent a cost-effective method for identifying potential therapeutic candidates capable of addressing these challenges (Sliwoski *et al*., 2014) [40].

The molecular dynamics simulations performed in this study further validated the stability of the ligand–protein complexes. The persistent hydrogen bonding interactions observed for Bavachin with Tyr435 in MAO-B and His278 in AA2AR throughout the 100-ns simulation support the reliability of the docking predictions. Such dynamic stability is consistent with previously reported binding behaviour of established inhibitors and strengthens the hypothesis that prenylated flavonoids may function as dual-target modulators.

Despite these promising findings, several limitations should be acknowledged. The present investigation relies entirely on computational predictions, which are inherently dependent on the accuracy of structural models, force fields, and simulation parameters. Additionally, the 100-ns molecular dynamics simulations may not capture all long-term conformational changes occurring *in vivo*. Experimental validation through enzyme inhibition assays, receptor binding studies, and cellular neuroprotection models will therefore be essential to confirm the pharmacological potential of the identified compounds.

Future research should focus on evaluating the MAO-B inhibitory activity of Bavachin and Bavachinin through *in vitro* enzyme assays, determining their selectivity against MAO-A, and assessing their neuroprotective effects in dopaminergic neuronal models. Structure–activity relationship studies and semi-synthetic modifications of the prenylated flavanone scaffold may further enhance potency and receptor specificity. Such efforts could ultimately contribute to the development of novel multi-target therapeutics capable of slowing or preventing the progression of Parkinson’s disease.

Conclusion

This study presents a multi-stage in silico investigation identifying Bavachin and Bavachinin as the most promising flavonoid-based dual inhibitors of MAO-B and adenosine A2A receptor for Parkinson's disease therapy. Both prenylated flavanones surpassed the reference drug Safinamide across molecular docking, MM-GBSA rescoring, and 100 ns MD stability endpoints, while satisfying all drug-likeness and blood–brain barrier permeability criteria. The structural features underpinning this performance — the lipophilic prenyl chain and hydrogen-bond-competent chromone core — provide actionable insights for rational semi-synthetic analogue design. These supportive computational predictions establish Bavachin and Bavachinin as priority candidates for experimental validation, and contribute to the growing evidence base for flavonoid-derived multi-target therapeutics in Parkinson's disease.

Declarations

Author Contributions

Rajeshwar Kaitwad and Ashish Gulwe contributed to the conceptualization, literature review, and drafting of the manuscript. All authors read and approved the final manuscript.

Competing Interests: The authors declare no competing interests.

Ethical Approval: This article contains no studies with human participants or animals.

Author Contributions: All authors contributed equally to study design, analysis, and writing.

Funding: No external funding was received for this study.

Data Availability: All datasets supporting this article are available within the article and supplementary files.

References

1. Abdelsayed M. AI-Driven Polypharmacology in Small-Molecule Drug Discovery. International Journal of Molecular Sciences. 2025; 26(14):6996. Doi: https://doi.org/10.3390/ijms26146996
2. Adhikary K, Ganguly K, Sarkar R, Abubakar M, Banerjee P, Karak P. Phytonutrients and their neuroprotective role in brain disorders. Frontiers in Molecular Biosciences. 2025; 12:1607330. Doi: https://doi.org/10.3389/fmolb.2025.1607330
3. Atanasov AG, Waltenberger B, Pferschy-Wenzig E-M, Linder T, Wawrosch C, Uhrin P, *et al*. Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnology Advances. 2015; 33(8):1582-1614. Doi: https://doi.org/10.1016/j.biotechadv.2015.08.001
4. Atanasov AG, Zotchev SB, Dirsch VM, The International Natural Product Sciences Taskforce, Orhan IE, Banach M, *et al*. Natural products in drug discovery: Advances and opportunities. Nature Reviews Drug Discovery. 2021; 20(3):200-216. Doi: https://doi.org/10.1038/s41573-020-00114-z
5. Bette S, Shpiner DS, Singer C, Moore H. Safinamide in the management of patients with Parkinson’s disease not stabilized on levodopa: A review of the current clinical evidence. Therapeutics and Clinical Risk Management. 2018; 14:1737-1745. Doi: https://doi.org/10.2147/TCRM.S139545
6. Cemali SH, Poyraz S, Belveren S, Taş S, Tamer MA, Döndaş NY, *et al*. Recent Insights in Multi-Target Drugs in Pharmacology and Medicinal Chemistry. ChemMedChem. 2025; 20(18):e202500447. Doi: https://doi.org/10.1002/cmdc.202500447
7. Chakrabarti S, Bisaglia M. Oxidative Stress and Neuroinflammation in Parkinson’s Disease: The Role of Dopamine Oxidation Products. Antioxidants. 2023; 12(4):955. Doi: https://doi.org/10.3390/antiox12040955

8. Chaudhary SA, Chaudhary S, Rawat S. Understanding Parkinson's disease: Current trends and its multifaceted complications. Frontiers in Aging Neuroscience. 2025; 17:1617106. Doi: https://doi.org/10.3389/fnagi.2025.1617106
9. Daina A, Michielin O, Zoete V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific Reports. 2017; 7(1):42717. Doi: https://doi.org/10.1038/srep42717
10. Dash UC, Bhol NK, Swain SK, Samal RR, Nayak PK, Raina V, *et al*. Oxidative stress and inflammation in the pathogenesis of neurological disorders: Mechanisms and implications. Acta Pharmaceutica Sinica B. 2025; 15(1):15-34. Doi: https://doi.org/10.1016/j.apsb.2024.10.004
11. Dias V, Junn E, Mouradian MM. The Role of Oxidative Stress in Parkinson's Disease. Journal of Parkinson's Disease. 2013; 3(4):461-491. Doi: https://doi.org/10.3233/JPD-130230
12. Dong-Chen X, Yong C, Yang X, Chen-Yu S, Li-Hua P. Signaling pathways in Parkinson's disease: Molecular mechanisms and therapeutic interventions. Signal Transduction and Targeted Therapy. 2023; 8(1):73. Doi: https://doi.org/10.1038/s41392-023-01353-3
13. Dorsey ER, Elbaz A, Nichols E, Abbasi N, Abd-Allah F, Abdelalim A, *et al*. Global, regional, and national burden of Parkinson's disease, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2018; 17(11):939-953. Doi: https://doi.org/10.1016/S1474-4422(18)30295-3
14. Feng B, Zhang J, Zhang X, Zhang M, Barth P, Liu Z, *et al*. Physically Grounded Generative Modeling of All-Atom Biomolecular Dynamics. Bioinformatics, 2026. Doi: https://doi.org/10.64898/2026.02.15.705956
15. Gao X, Cassidy A, Schwarzschild MA, Rimm EB, Ascherio A. Habitual intake of dietary flavonoids and risk of Parkinson disease. Neurology. 2012; 78(15):1138-1145. Doi: https://doi.org/10.1212/WNL.0b013e31824f7fc4
16. Hashem S, Ali TA, Akhtar S, Nisar S, Sageena G, Ali S, *et al*. Targeting cancer signaling pathways by natural products: Exploring promising anti-cancer agents. Biomedicine & Pharmacotherapy. 2022; 150:113054. Doi: https://doi.org/10.1016/j.biopha.2022.113054
17. Hinz S, Navarro G, Borroto-Escuela D, Seibt BF, Ammon Y-C, De Filippo E, *et al*. Adenosine A2A receptor ligand recognition and signaling is blocked by A2B receptors. Oncotarget. 2018; 9(17):13593-13611. Doi: https://doi.org/10.18632/oncotarget.24423
18. Jomova K, Alomar SY, Valko R, Liska J, Nepovimova E, Kuca K, *et al*. Flavonoids and their role in oxidative stress, inflammation, and human diseases. Chemico-Biological Interactions. 2025; 413:111489. Doi: https://doi.org/10.1016/j.cbi.2025.111489
19. Joshi OV, Savale RR, Nalage D, Biradar A, Sontakke T. Lifestyle in flux: Urbanization, dietary shifts, and endocrine health in emerging adulthood. Reproductive Biology and Endocrinology: RB&E. 2025; 23(1):118. Doi: https://doi.org/10.1186/s12958-025-01442-8
20. Kaitwad R, Gulwe A, Dipke C, Suryawanshi H, Murge N, Nalage D. Current and emerging therapies for Parkinson's disease: Advances toward disease modification. Life Research. 2025; 8(4):22. Doi: https://doi.org/10.53388/LR20250022
21. Kouli A, Torsney KM, Kuan W-L. Parkinson's Disease: Etiology, Neuropathology, and Pathogenesis. In T. B. Stoker & J. C. Greenland (Eds.). Parkinson's Disease: Pathogenesis and Clinical Aspects. Codon Publications, 2018. http://www.ncbi.nlm.nih.gov/books/NBK536722/
22. Kruszka J, Martyński J, Szewczyk-Golec K, Woźniak A, Nuszkiewicz J. The Role of Selected Flavonoids in Modulating Neuroinflammation in Alzheimer's Disease: Mechanisms and Therapeutic Potential. Brain Sciences. 2025; 15(5):485. Doi: https://doi.org/10.3390/brainsci15050485
23. Kumar S, Nalage DN, Aslam M, Singh S, Kumar U. Evaluation of Bloodstream Infections Associated with Carbapenem-Resistant Enterobacteriaceae in Paediatric and Adult Patients. Egyptian Journal of Veterinary Sciences. 2025; 0(0):1-8. Doi: https://doi.org/10.21608/ejvs.2025.319804.2373
24. Latif R, Nawaz T. Medicinal plants and human health: A comprehensive review of bioactive compounds, therapeutic effects, and applications. Phytochemistry Reviews, 2025. Doi: https://doi.org/10.1007/s11101-025-10194-7
25. Lv H-W, Wang Q-L, Luo M, Zhu M-D, Liang H-M, Li W-J, *et al*. Phytochemistry and pharmacology of natural prenylated flavonoids. Archives of Pharmacal Research. 2023; 46(4):207-272. Doi: https://doi.org/10.1007/s12272-023-01443-4
26. Mateev E, Pavlova E, Kostov S, Irfan A, Mateeva A, Kondeva-Burdina M, *et al*. Multi-target monoamine oxidase-B (MAO-B) inhibitors in the treatment of Parkinson's disease. Pharmacia. 2025; 72:1-19. Doi: https://doi.org/10.3897/pharmacia.72.e164727
27. Müller T. The safety of istradefylline for the treatment of Parkinson's disease. Expert Opinion on Drug Safety. 2015; 14(5):769-775. Doi: https://doi.org/10.1517/14740338.2015.1014798
28. Murakami H, Shiraishi T, Umehara T, Omoto S, Iguchi Y. Recent Advances in Drug Therapy for Parkinson's Disease. Internal Medicine. 2023; 62(1):33-42. Doi: https://doi.org/10.2169/internalmedicine.8940-21
29. Naik RA, Rajpoot R, Koiri RK, Bhardwaj R, Aldairi AF, Johargy AK, *et al*. Dietary supplementation and the role of phytochemicals against the Alzheimer's disease: Focus on polyphenolic compounds. The Journal of Prevention of Alzheimer's Disease. 2025; 12(1):100004. Doi: https://doi.org/10.1016/j.tjpad.2024.100004
30. Nalage DN, Khedkar GD, Kalyankar AD, Sarkate AP, Ghodke SR, Bedre VB, *et al*. Single Cell Proteins. In Encyclopedia of Food and Health. Elsevier, 2016, 790-794. Doi: https://doi.org/10.1016/B978-0-12-384947-2.00628-0
31. Nalage DN, Kudnar PS, Langhe R, Ughade B, Sontakke T, Biradar A. Leukemia in India: Insights Into Incidence, Prevalence, Mortality, and Disability-Adjusted Life Years. Cureus, 2024. Doi: https://doi.org/10.7759/cureus.62557
32. Nalage D, Sontakke T, Biradar A, Jogdand V, Kale R, Harke S, *et al*. The impact of environmental toxins on the animal gut microbiome and their potential to contribute to disease. Elsevier. 2023; 3(C).

33. Nalage D, Sontakke T, Patil R, Ughade B, Biradar A. First Three Days of Life. Zenodo, 2022. Doi: https://doi.org/10.5281/ZENODO.7703485
34. Nasim N, Sandeep IS, Mohanty S. Plant-derived natural products for drug discovery: Current approaches and prospects. The Nucleus: An International Journal of Cytology and Allied Topics. 2022; 65(3):399-411. Doi: https://doi.org/10.1007/s13237-022-00405-3
35. Patil R, Satpute R, Nalage D. The application of omics technologies to toxicology. Toxicology Advances. 2023; 5(2):6. Doi: https://doi.org/10.53388/TA202305006
36. Patil R, Sontakke T, Biradar A, Nalage D. Zinc: An essential trace element for human health and beyond. Food and Health. 2023; 5(3):13. Doi: https://doi.org/10.53388/FH2023013
37. Qasaymeh RM, Rotondo D, Oosthuizen CB, Lall N, Seidel V. Predictive Binding Affinity of Plant-Derived Natural Products Towards the Protein Kinase G Enzyme of Mycobacterium tuberculosis (MtPknG). Plants. 2019; 8(11):477. Doi: https://doi.org/10.3390/plants8110477
38. Rao P, Rathinaswamy M, Chan M, Paredes AG, Patel C, Wranik BJ, *et al*. Systematic metabolite screening identifies functional regulators of the adenosine A2A receptor. Communications Chemistry. 2025; 9(1):19. Doi: https://doi.org/10.1038/s42004-025-01825-3
39. Sharma P, Singh S, Kumar U, Nalage DN. Prevalence of Cancer in India with Respect to Leukaemia and their Factorial Relations. Defence Life Science Journal. 2025; 10(2):90-100. Doi: https://doi.org/10.14429/dlsj.10.20126
40. Sliwoski G, Kothiwale S, Meiler J, Lowe EW. Computational Methods in Drug Discovery. Pharmacological Reviews. 2014; 66(1):334-395. Doi: https://doi.org/10.1124/pr.112.007336
41. Sontakke T, Biradar A, Dixit P, Nalage D. Metagenomics and microbiome of infant: Old and recent instincts. Microenvironment and Microecology Research. 2022; 4(2):7. Doi: https://doi.org/10.53388/MMR2022007
42. Sontakke T, Biradar A, Nalage D. The role of genetics in determining resistance to coccidiosis in goats a review of current research and future directions. Molecular Biology Reports. 2023; 50(7):6171-6175. Doi: https://doi.org/10.1007/s11033-023-08520-3
43. Stachelska MA, Karpiński P, Kruszewski B. A Comprehensive Review of Biological Properties of Flavonoids and their Role in the Prevention of Metabolic, Cancer and Neurodegenerative Diseases. Applied Sciences. 2025; 15(19):10840. Doi: https://doi.org/10.3390/app151910840
44. Tan Y-Y, Jenner P, Chen S-D. Monoamine Oxidase-B Inhibitors for the Treatment of Parkinson's Disease: Past, Present, and Future. Journal of Parkinson's Disease. 2022; 12(2):477-493. Doi: https://doi.org/10.3233/JPD-212976
45. Wang E, Weng G, Sun H, Du H, Zhu F, Chen F, *et al*. Assessing the performance of the MM/PBSA and MM/GBSA methods. 10. Impacts of enhanced sampling and variable dielectric model on protein-protein Interactions. Physical Chemistry Chemical Physics. 2019; 21(35):18958-18969. Doi: https://doi.org/10.1039/C9CP04096J
46. Wong T-S, Li G, Li S, Gao W, Chen G, Gan S, *et al*. G protein-coupled receptors in neurodegenerative diseases and psychiatric disorders. Signal Transduction and Targeted Therapy. 2023; 8(1):177. Doi: https://doi.org/10.1038/s41392-023-01427-2
47. Zhang X, Molsberry SA, Yeh T-S, Cassidy A, Schwarzschild MA, Ascherio A, *et al*. Intake of Flavonoids and Flavonoid-Rich Foods and Mortality Risk Among Individuals With Parkinson Disease: A Prospective Cohort Study. Neurology. 2022; 98(10). Doi: https://doi.org/10.1212/WNL.0000000000013275