

Original Research Article

Exploring the neuroprotective effects of Pterostilbene against rotenone-induced Parkinson's disease in Zebra Fish: An integrated *in silico* and *in vivo* approach

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Abstract

Purpose: To investigate the neuroprotective potential of pterostilbene (a natural dietary compound found primarily in blueberries and other small fruits) against rotenone-induced Parkinson's disease (PD) in zebrafish.

Methods: Rotenone-induced Parkinson's disease was modeled in adult male Zebrafish using 5 µg/L rotenone via static immersion for 21 days. Pterostilbene was co-administered at 125 µg/L and 250 µg/L. Molecular docking was used to assess the affinity of pterostilbene for monoamine oxidase (MAO), while molecular dynamics evaluated the complex stability. Behavioral tests and biochemical analyses were conducted on day 22 to assess neuroprotection.

Results: Treatment with pterostilbene significantly enhanced locomotor activity and reduced anxiety-like behaviors in Zebrafish exposed to rotenone ($p < 0.0001$). Also, pterostilbene significantly inhibited dopaminergic neuronal degeneration and neuroinflammation in a dose-dependent manner ($p < 0.001$).

Conclusion: Pterostilbene significantly enhances motor activity, reduces anxiety-like behaviours, inhibits dopaminergic neuronal degeneration, and inflammation. Further studies into the kinetics of pterostilbene and adjusted dosing regimens would be required before clinical trials.

Keywords: Antioxidants, Zebra fish model, Parkinson's disease, Pterostilbene, Neuroprotection

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INTRODUCTION

Parkinson's disease (PD) is a chronic neurological condition primarily marked by gradual loss of dopamine-producing neurons in the substantia nigra region of the brain. This leads to hallmark motor symptoms such as slowness of movement, muscle stiffness,

tremors, and impaired balance [1]. The disease is influenced by a combination of genetic factors, environmental exposures, and lifestyle choices. These contribute to cellular damage through mechanisms including oxidative stress, impaired mitochondrial function, and inflammation in the nervous system [2]. Despite progress in understanding its molecular basis, most current

therapies focus on symptom control rather than halting disease progression. Moreover, long-term use of standard medications often results in side effects like motor fluctuations and involuntary movements, reinforcing the need for treatments that target the root causes of the neuronal degeneration [3].

Recent studies have shifted attention to naturally derived compounds due to their potential neuroprotective effects on nerve cells. Among these, pterostilbene (a compound found in blueberries, grapes, and Indian Kino tree) has shown promising results due to its antioxidant, anti-inflammatory, and cell-protecting properties [4]. Compared to its structural relative resveratrol, pterostilbene has better absorption and stability in the body and crosses the blood-brain barrier efficiently, making it a suitable candidate for neurological treatment [5]. In this study, the neuroprotective effect of pterostilbene was investigated using a zebrafish model in which PD-like symptoms were induced by rotenone, a pesticide known to disrupt mitochondrial function and increase the production of harmful reactive oxygen species [6]. Zebrafish were chosen due to their genetic similarity to humans, rapid development, and suitability for observing disease mechanisms in real time [7].

Computational tools were used to predict the interaction between pterostilbene and other plant-based molecules with key proteins involved in PD. Docking studies against monoamine oxidase enzymes were performed, followed by molecular dynamics simulations to assess the stability of these interactions [8]. Analyses included measurements of protein flexibility, surface exposure, and structural changes, along with energy calculations to evaluate binding strength.

EXPERIMENTAL

In silico studies, docking protocol

This work comprises molecular docking with AutoDock Vina (PMID: 19499576) on 16 phytochemicals and 1 FDA-approved medicine against human monoamine oxidases with PDB ID 2C67 (PMID: 16366596). The 3D configurations of the phytochemicals and pharmaceuticals were acquired from PubChem (PMID: 33151290) and processed for docking using Open Babel software (PMID: 21982300). Similarly, the receptor, Human Monoamine Oxidase PDB ID 2C6, was ready for docking. AutoDock Vina parameters, including search space and grid box dimensions set at 8 x 10 x

10, were configured and docking runs were launched. The resulting docking poses were evaluated for binding strength, and the top docking configurations were chosen for continued studies [9]. Binding processes and interactions between ligands and receptors were studied using PyMOL software (PMID: 20401516). Findings from the docking study were employed to evaluate the efficiency of the phytochemicals and pharmaceuticals as inhibitors of the human monoamine oxidase enzyme.

Molecular dynamics

A molecular dynamics (MD) simulation was conducted using Gromacs software program, a widely established tool for MD simulations. The protein-ligand complex was lowered in a vacuum using the steepest descent technique. Subsequently, the complex was immersed in a periodic box of water using the SPC water model, representing water molecules as single-point charges. Sodium and chloride ions were administered to maintain a salt concentration of 0.15 M under normal pressure and temperature (NPT). A 100 ns manufacturing run was done in the NPT ensemble to accurately simulate parameters of a biological system at ambient temperature and pressure. The study uses multiple Gromacs techniques, including RMSD, RMSF, RG, SASA, and H-Bond for trajectory analysis. This was aimed at investigating the structural and dynamic characteristics of the system, including shape, flexibility, and interactions with the solvent [10].

The strategy includes finishing MMPBSA computations on the target complex and utilizing the final 50 ns of Gromacs trajectories. Elaborate arrangements were made for computing in Gromacs, which include the incorporation of solvents and the building of topological files. Configuration for MMPBSA computation was performed using the MMPBSA software, with energy decomposition accomplished on each complex during the last 50 ns trajectory. The obtained energy components were assessed to measure the binding affinity and contributions of various energy terms to the overall binding energy.

In vivo evaluation

The Zebrafish experiments were conducted in a Good Laboratory Practice (GLP)-certified facility. The zebrafish (*Danio rerio*) were housed in 4-liter tanks equipped with continuous filtration and aeration systems under standard environmental conditions (stable pH of 7.5, dissolved oxygen

levels above 60 %, and temperature of 26 ± 1 °C, and 14:10 hour light / dark cycle). The fish was allowed one-week acclimatization period prior to experimentation. The maximum housing density was limited to two fish per liter. The animals were fed a combination of commercially available flakes three times daily and live brine shrimp obtained from a local supplier. Dechlorinated water was consistently used throughout the study [11]. For the experimental phase, adult male zebrafish aged between 6 – 8 months were selected. The study included a total of 60 male zebrafish, divided into five groups which include a group 1 (control group), group 2 (rotenone-induced group), group 3 (a standard treatment group receiving both rotenone [12] and rasagiline (used as the reference drug)), groups 4 and 5 received rotenone with pterostilbene at 125 and 250 µg/L, respectively [13].

Ethical approval was obtained from the Institutional Animal Ethical Committee (IAEC) at Sri Ramachandra Institute (approval no. IAEC/69/SRIHER/826/2023) and in accordance with the standards set by the Animal Testing Regulatory Board. The study adhered to the Organization for Economic Co-operation and Development (OECD) Guideline 203 [14].

Limit test

A 96-hour limit test was conducted using the water static method during which the test drug was administered at a concentration of 100 mg/L. The median lethal concentration (LC_{50}) was determined, and the test was considered valid if mortality in the control group did not exceed 10 % [15].

Treatment

Following acclimatization, the zebrafish were exposed daily to the respective treatments using the static method for 21 days. Control group received 0.1 % dimethyl sulfoxide (DMSO), group 2 (rotenone-only group) received rotenone without any treatment, group 3 received a combination of rotenone and rasagiline, groups 4 and 5 received rotenone with pterostilbene at 250 µg/L and 125 µg/L. On the 22nd day, neurobehavioral analysis was conducted on all groups except control group. Each group was maintained in labeled tanks, and exposure procedure was carried out daily using the same static method [16].

Neurobehavioral analysis

On day 22, the animals underwent neurobehavioral analysis, including locomotor

activity, anxiety and stress evaluation, anti-social, and aggression tests. A total of 5 fish from each group participated in the Novel Tank Diving Experiment (NTDT). A transparent glass tank, divided horizontally into upper and lower sections, was further partitioned vertically into 4 zones, each measuring 6 cm in length. The fish were transferred into a new tank, and locomotor activity was observed for 5 min in this modified environment by the number of lines crossed. Subsequently, they were placed in individual housing. Parameters such as interval within the upper and lower zones, latency to enter the upper zones, transitions between zones, and total distance traveled were recorded to evaluate locomotor activity, anxiety, and stress levels in the novel tank environment [17].

Anti-social and aggressive test

At the end of the experimental period, a total of 5 zebrafishes from each group were subjected to behavioral testing to evaluate antisocial and aggressive tendencies. A modified behavioral assay was employed, which involved placing a mirror on the right side of the testing arena, following a standardized protocol [18]. A fish's tendency to focus on the mirror (right side) was interpreted as an indicator of aggression, while attention directed toward the left side (away from the mirror) was considered antisocial behavior. Each fish was given a one-minute acclimatization period before the test, and each trial lasted for 5 min. Behavioral parameters recorded include the number of aggressive episodes, latency to first mirror contact, frequency of aggressive interactions, and behavioral responses on the side without the mirror. This modified testing approach enabled clear assessment and quantification of antisocial and aggressive behaviors, offering valuable insight into social interactions and behavioral changes of zebrafish under different experimental conditions.

Biochemical studies

Myeloperoxidase assay

Following completion of the neurobehavioral assessments, zebrafish from all experimental groups were euthanized using an overdose of tricaine methane sulfonate (300 mg/L). The brains were carefully extracted and immediately processed for biochemical analysis. Brain tissues were homogenized using a mechanical homogenizer (Fisher Scientific, Waltham, MA) in 500 µL cetyltrimethylammonium bromide (CTAB) buffer, which consisted of 50 mM CTAB (Sigma-Aldrich, USA) dissolved in 50 mM potassium phosphate buffer (pH 6.0). The homogenates

were sonicated and centrifuged at 15,000 rpm for 20 min. The resulting supernatant, containing soluble proteins, was subjected to protein precipitation by centrifugal separation at 3,500 rpm for 15 min at 4 °C. The precipitated proteins were air-dried at room temperature and reconstituted in phosphate-buffered saline (PBS) for evaluation of myeloperoxidase (MPO) enzyme activity using a colorimetric assay with 3,3',5,5'-tetramethylbenzidine (TMB) (Sigma-Aldrich, USA). Each sample (10 µL) was mixed with 80 µL 0.75 mM hydrogen peroxide (Sigma-Aldrich, USA) and 110 µL TMB solution (2.9 mM TMB in 14.5 % DMSO and 150 mM sodium phosphate buffer, pH 5.4). The reaction mixture was incubated at 37 °C for 5 min, after which 100 µL of 2 M sulfuric acid (Sigma-Aldrich, USA) was added to stop the reaction. Absorbance was measured at 450 nm to quantify MPO activity across all groups [19].

Dopamine assay

After conducting a neurobehavioral examination on the fish using 160 mg/L ice-cold tricaine methanesulfate, pH 7.0, the fish were euthanized, and the brain was immediately dissected and homogenized using lysis buffer while still cool. Dopamine concentrations in the brain supernatant were assessed using high-performance liquid chromatography-mass – spectrometry (HPLC-MS). The standard drug, Rasagiline, was dissolved in 0.1 N perchloric acid (1.0 mL) to create stock-standard solutions. All solutions were stored in the dark at -24 °C and further diluted with water to the necessary concentrations before use, sustaining stability for at least a month. Distilled water was added to either the conventional solution or the filtrate made from brain homogenization. An internal standard, DHBA (3,4-Dihydroxybenzylamine), was added (50 µL) and a concentration of 200 ng/mL. After the addition of 20 µL ethyl chloroformate and a 4:1 (v/v) combination of ethanol and pyridine, the reaction was agitated for 3 min. Diethyl ether (1 mL) was then added to the mixture, subsequently refrigerated at -40 °C, and stirred on a vortex mixer for 2 min. Following solvent evaporation in a vacuum oven, the organic component was transferred to another tube. The acquired residue was dissolved in acetonitrile (50 µL), and 5 µL of the resultant solution was instilled into the HPLC-MS [20].

Statistical analysis

Data analysis was conducted using GraphPad Prism version 9.5.1 (GraphPad Software, San Diego, CA, USA). Results were expressed as mean ± standard deviation (SD) and compared

using Dunnett's test and one-way analysis of variance (ANOVA). $P < 0.0001$ was considered statistically significant.

RESULTS

Molecular docking

Molecular docking studies revealed that the phytochemicals kaempferol, hesperetin, naringenin, and pterostilbene exhibited strong inhibitory potential against human monoamine oxidase. Among them, naringenin (-9.6 kcal/mol) and pterostilbene (-9.5 kcal/mol) showed the strongest binding affinities, outperforming the standard drug rasagiline (-7.7 kcal/mol). Lower (more negative) binding energies indicate stronger interactions. While kaempferol and hesperetin did not exceed naringenin and pterostilbene, they still showed better affinity compared to rasagiline. These are structurally distinct compounds, interacting primarily through hydrophobic forces (Table 1).

Table 1: Binding affinity of various compounds against the human monoamine oxidase enzyme

Compound	Binding affinity (kcal/mole)
Standard (Rasagiline)	-7.7
Naringenin	-9.6
Pterostilbene	-9.5

Molecular dynamics (MD)

The simulation provides insights into the binding behavior of the inhibitor with target protein, its impact on protein activity, molecular interaction sites and inhibitory pathways. Various structures were analyzed to observe the variable patterns of the target protein: (i) the protein alone [APO], (ii) the protein in complex with Naringenin (NAG), (iii) the protein in complex with Pterostilbene (PTE), and (iv) the protein in complex with Rasagiline (RAS).

Root mean square deviation (RMSD)

The RMSD values for protein complexes were analyzed over a 100-ns simulation period. The RMSD of APO complex was 0.31 ± 0.035 nm, NAG complex was 0.29 ± 0.069 nm, PTE complex was 0.29 ± 0.16 nm, RAS complex was 0.29 ± 0.069 nm. These values indicated very little structural change in the protein complexes during simulation. Generally, the complexes demonstrated good stability with minimal differences, likely due to structural similarities between the compounds (Figure 1).

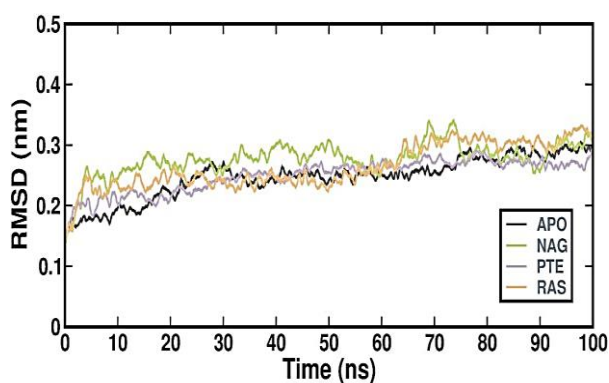


Figure 1: RMSD of backbone atoms of APO, NAG, PTE, and RAS

Root mean square fluctuation (RMSF)

The RMSF values were computed over 100 ns to monitor changes in protein dynamics as a function of time. The RMSF outputs for the APO, NAG, PTE, and RAS complexes showed no dramatic changes in structure over the 100 ns simulation.

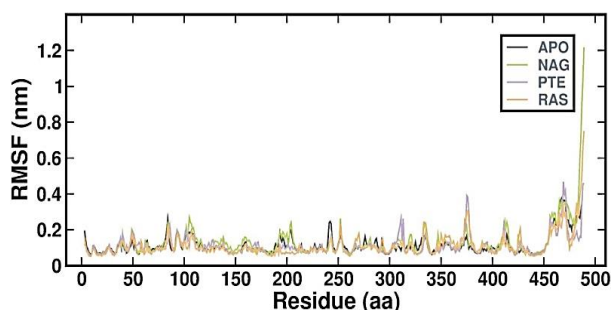


Figure 2: RMSF of c-alpha atoms of APO, NAG, PTE, and RAS

Radius of gyration (RG)

Radius of gyration (Rg) describes the compactness of a protein's conformation, representing the mass-weighted average distance of atoms from the center of mass. The Rg values for APO, NAG, PTE, and RAS complexes were 2.28 ± 0.014 nm, 2.29 ± 0.019 nm, 2.28 ± 0.019 nm, and 2.29 ± 0.018 nm, respectively. These Rg measurements indicated good retention of structural integrity and limited flexibility within the protein complexes throughout the simulation, suggesting that the protein complexes maintained their folded form consistently.

Solvent accessible surface area (SASA)

Changes in SASA specifically for the protein's hydrophobic core were monitored to study its structural stability (Figure 4). The average SASA values for APO, NAG, PTE, and RAS protein

complexes were 221.01 ± 4.45 nm², 228.46 ± 3.51 nm², 225.16 ± 5.61 nm² and 231.17 ± 2.81 nm², respectively. These SASA values suggest that the structural stability of these proteins remained largely unchanged, indicating consistent exposure of the hydrophobic core to the solvent across all complexes throughout simulation (Figure 4).

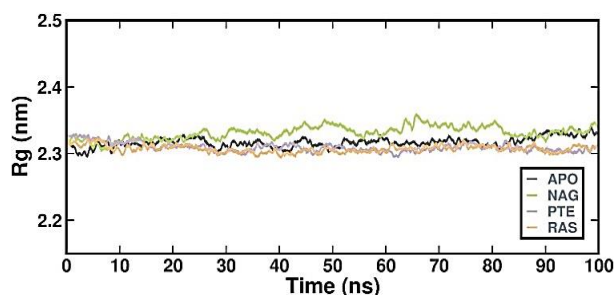


Figure 3: Rg of backbone atoms with APO, NAG, PTE, and RAS

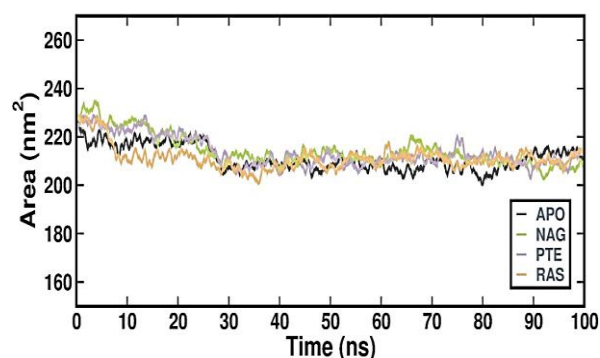


Figure 4: The SASA of the backbone atoms of the protein is shown in four different states

Hydrogen bond (H-bond)

Consistency of protein-ligand complexes is often linked to the formation of hydrogen bonds between the protein and the ligand. In this study, hydrogen bonds identified during the molecular docking analysis were confirmed through additional simulation-based validation (Figure 5).

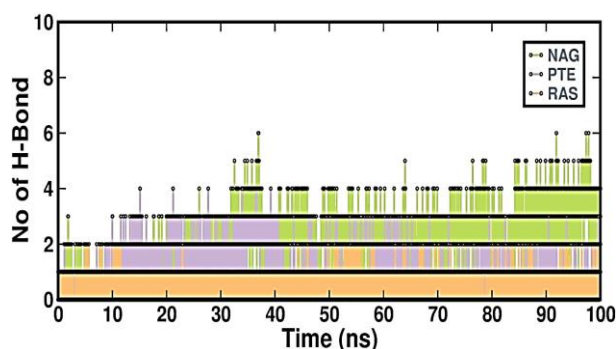


Figure 5: H-bond of NAG, PTE, and RAS

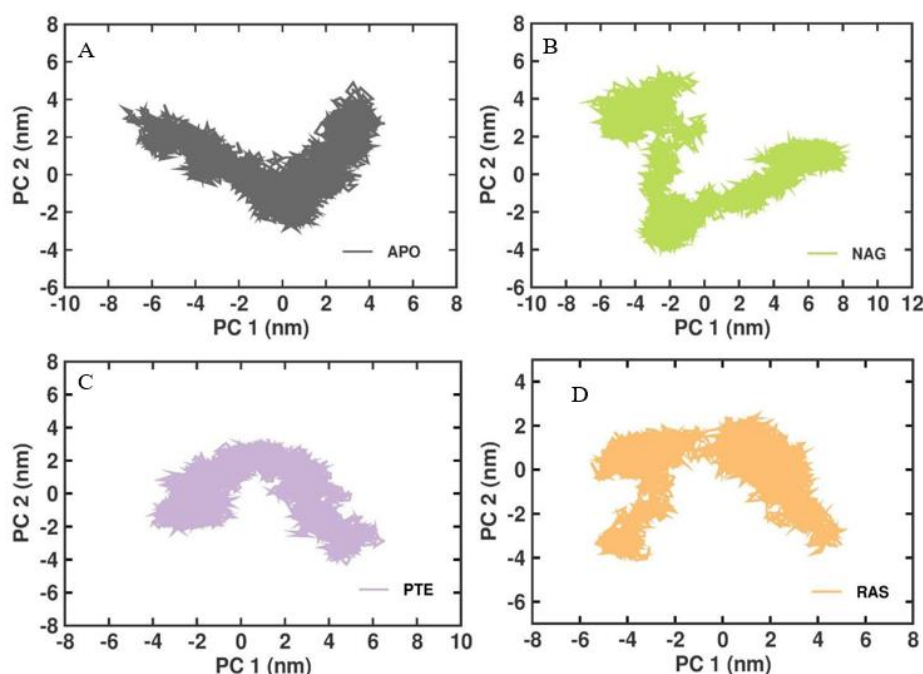


Figure 6: Principal component analysis (PCA) of APO (A), NAG (B), PTE (C), and RAS (D)

Principal component analysis (PCA)

Principal component analysis (PCA) is a statistical method applied to lower data complexity and discover key features or patterns. Widely used in structural biology, PCA aids in studying conformational variations in proteins or protein-ligand complexes. In this study, PCA was conducted on the APO (Figure 6 A), NAG (Figure 6 B), PTE (Figure 6 C), and RAS (Figure 6 D) complexes to investigate structural disparities among the protein samples.

MM-PPBSA

Relative strength and binding affinity of NAG, PTE, and RAS were evaluated through summative energy (Table 2).

Table 2: Relative strength and binding affinity

System	Van der Waal energy (kJ/mol)	Electrostatic energy (kJ/mol)	Polar solvation energy (kJ/mol)	Binding energy (kJ/mol)
NAG	-139.708±7.076	-111.343±13.367	209.324±6.512	-57.769±20.735
PTE	-163.201±12.576	-31.847±7.611	115.785±13.995	-97.114±16.939
RAS	-126.628±5.718	-9.832±3.691	69.225±11.608	-80.722±11.453

Table 3: Locomotor activity, anxiety, and stress evaluation

Group	Time spent in top area (s)	Time spent at the bottom (s)	Latency to enter the top area (s)	Transition to the top area (s)	Total distance travelled (cm/5min)
1	199.40±13.03	100.60±13.03	40.00±8.50	12.40±1.63	999.60±205.60
2	44.40±11.53 ^d	255.60±11.53 ^d	151.60±20.93 ^d	2.00±0.63 ^d	223.60±48.65 ^d
3	86.40±12.72 ^d	213.60±12.72 ^d	94.00±13.59 ^c	6.00±1.67 ^d	260.80±38.99 ^d
4	132.60±9.78 ^d	167.40±9.78 ^d	59.80±12.29 ^d	9.40±1.74 ^b	301.20±47.50 ^d
5	104.00±0.80 ^d	195.20±16.00 ^d	94.80±17.20 ^a	7.20±2.56 ^c	263.80±37.43 ^d

Neurobehavioral analysis

Treatment with pterostilbene resulted in significantly improved locomotor activity at 125 and 250 µg/L compared to control group ($p < 0.0001$). At higher dose (250 µg/L), there was significant improvement in total distance travelled ($p < 0.05$), however, lower than the standard group in other measures.

Number of aggressivity episodes

Treatment with rasagiline resulted in a significant reduction in the number of aggression episodes ($p < 0.001$), extended latency ($p < 0.0001$), and fewer aggressive episodes ($p < 0.01$) compared to group 2.

Table 4: Number of aggressive episodes and other related parameters

Group	Number of aggression episodes (s)	Latency of mirror contact (s)	Aggressive episode(s)	Non-mirror side (s)
1	7.00±1.90	82.20±14.55	146.20±26.99	153.80±26.99
2	52.00±11.59 ^d	4.40±1.85 ^d	233.00±27.61 ^a	67.00±27.61 ^d
3	28.00±4.05 ^c	20.40±4.08 ^d	208.20±33.11 ^b	91.80±33.11 ^c
4	17.20±2.64 ^c	26.40±3.44 ^d	181.80±23.80 ^b	118.20±23.80 ^b
5	29.00±4.52 ^a	17.60±4.13 ^d	195.40±45.00 ^a	104.60±45.00 ^c

Furthermore, treatment with pterostilbene significantly reduced number of aggression episodes ($p < 0.001$), higher latency ($p < 0.0001$), and fewer aggressive episodes ($p < 0.01$), suggesting better anti-aggressive efficacy compared to rasagiline in a dose-dependent manner (Table 4).

Biochemical activity

Group 2 showed significantly elevated MPO activity and dopamine levels compared to control ($p < 0.0001$), indicating increased inflammatory response. Treatment with rasagiline (standard group) showed significant reduction in MPO and dopamine levels compared to group 2 ($p < 0.001$). Furthermore, treatment with pterostilbene at 250 µg/L significantly reduced dopamine levels compared to control and group 2 ($p < 0.0001$), indicating a strong inhibitory effect. However, MPO levels remained significantly elevated compared to control ($p < 0.0001$), though lower than group 2. These results suggest that while pterostilbene effectively suppressed dopamine levels, it had limited impact on inflammation compared to rasagiline (standard drug; Table 5).

Table 5: Biochemical analysis of myeloperoxidase and dopamine

Group	Myeloperoxidase (U/mg)	Dopamine (pg/mL)
1	0.80±0.04	13.13±0.10 ^d
2	1.27±0.08 ^d	19.32±0.09 ^d
3	1.05±0.03 ^c	10.00±1.41 ^d
4	1.11±0.16 ^d	6.29±0.14 ^d

DISCUSSION

The present study highlighted the neuroprotective potential of the phytochemicals, naringenin and pterostilbene, through their significant inhibitory effects on human monoamine oxidase (MAO), supported by molecular docking and molecular dynamics simulations. These findings are in tandem with growing evidence that flavonoids, such as naringenin and pterostilbene, exhibit MAO inhibitory activity, suggesting therapeutic roles in neurodegenerative disorders like Parkinson's and Alzheimer's diseases [20].

Previous studies have demonstrated similar MAO inhibition with flavonoids such as quercetin, luteolin, kaempferol, and hesperidin [21]. However, it is important to clarify that kaempferol and hesperidin were not part of the present study; hence, they were referenced only to support the broader relevance of flavonoids as MAO inhibitors. These compounds are chemically distinct from naringenin and pterostilbene and are not synonyms. Their inclusion serves to establish a background context, not to suggest their evaluation in the current study.

This study specifically evaluated naringenin and pterostilbene, both of which demonstrated superior molecular docking scores compared to the standard drug rasagiline. This suggests their potential as effective natural alternatives or adjuncts to synthetic MAO inhibitors. Also, molecular dynamics simulations confirmed the stability of these ligand-protein complexes, as shown by consistent values for radius of gyration and solvent-accessible surface area.

Supporting these *in silico* findings, the zebrafish model used in this study provided *in vivo* evidence of neurobehavioral benefits of the test compounds. Biochemical analyses further revealed that these compounds significantly decreased myeloperoxidase activity and modulated dopamine levels, supporting their anti-inflammatory and neuroprotective roles [22]. By integrating computational and experimental methods, this study substantiated the therapeutic promise of naringenin and pterostilbene as natural neuroprotective agents. Unlike other flavonoids mentioned for comparative context, these two compounds were directly evaluated and found to have significant potential in addressing key pathological features of neurodegenerative diseases.

CONCLUSION

Naringenin and pterostilbene demonstrate significant MAO inhibition and neuroprotective effects against rotenone-induced Parkinsonism in zebrafish model. This integrated computational and experimental approach provides detailed

insights into the mechanism of action and helps to deepen current understanding of how natural products like naringenin and pterostilbene may serve as therapeutic interventions for neurodegenerative diseases.

DECLARATIONS

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Availability of data and materials

The datasets utilized and/or analyzed in this study are available from the corresponding author upon reasonable request.

Ethical approval

Ethical approval was obtained from the Institutional Animal Ethical Committee (IAEC) at Sri Ramachandra Institute (approval no. IAEC/69/SRIHER/826/2023)

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

The authors confirm that this work was conducted by the individuals listed in this article, and they will assume full responsibility for any claims or liabilities related to the content of this article. All authors made substantial contributions to the manuscript, participated in review and editing, and approved the final version for publication.

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