

Aerobic exercise and resveratrol cooperatively modulate hippocampal mitochondrial mitophagy in Alzheimer's disease rat models

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Article Type: Research Article

Article History

Received: 9 March 2025

Received in revised form: 27 August 2025

Accepted: 10 September 2025

Available online: 23 September 2025

DOI: [10.29252/jorjanibiomedj.13.3.25](https://doi.org/10.29252/jorjanibiomedj.13.3.25)

Keywords

[Exercise Therapy](#)
[Resveratrol](#)
[Mitophagy](#)
[Hippocampus](#)
[Alzheimer Disease](#)



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Abstract

Background: Mitochondrial proteostasis disruption in Alzheimer's disease (AD) results in impaired mitochondrial autophagy (Mitophagy). This study evaluated the effects of 8-week aerobic exercise training (T), resveratrol (RSV) supplementation, and their combination on mitophagy markers in an AD rat model.

Methods: In this experimental study, 35 male Wistar rats were divided into five groups: Control (NO), Alzheimer's (AD), Alzheimer's-Training (ADT), Alzheimer's-Resveratrol (ADRSV), and Alzheimer's-Training-Resveratrol (ADTRSV). RSV groups received 20 mg/kg/day orally. The aerobic exercise protocol consisted of treadmill running (6-18 m/min) five days per week for eight weeks. Hippocampal PINK1 and PARKIN expression levels were analyzed.

Results: AD induction significantly reduced PINK1 and PARKIN expression (P-Value < 0.001). Compared to the AD group, significant increases in PINK1 and PARKIN were observed in the ADT (P-Value = 0.043; P-Value = 0.005), ADRSV (P-Value = 0.033; P-Value = 0.046), and ADTRSV (P-Value < 0.001) groups. The ADTRSV group showed higher PINK1 expression than ADT (P-Value = 0.036) and ADRSV (P-Value = 0.046), and greater PARKIN expression than ADRSV (P-Value = 0.046).

Conclusion: Exercise training and RSV supplementation improved hippocampal mitophagy in AD rats, with synergistic effects observed in the combined intervention. These findings suggest that non-pharmacological strategies may mitigate AD-related mitochondrial dysfunction.

Highlights

What is current knowledge?

- Mitochondrial dysfunction and impaired mitophagy are central features of Alzheimer's disease (AD), contributing to neuronal loss and cognitive decline.
- Aerobic exercise and resveratrol (RSV) supplementation have been independently reported to improve mitochondrial function and reduce oxidative stress.
- The PINK1/PARKIN signaling pathway regulates mitochondrial quality control through mitophagy.

What is new here?

- This study demonstrates that aerobic exercise and RSV synergistically enhance hippocampal mitophagy in AD rats.
- Combined intervention more effectively upregulated PINK1 and PARKIN gene expression compared with single treatments.
- Findings highlight the potential of integrating exercise and nutritional polyphenols as a multimodal non-pharmacological strategy against AD-related mitochondrial impairment.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder predominantly affecting the elderly, and is the most common cause of dementia worldwide (1). Clinically, AD is characterized by progressive memory loss, cognitive impairment, and functional decline. Pathologically, hallmark features include extracellular amyloid-beta (A β) plaques, intracellular neurofibrillary tangles composed of hyperphosphorylated tau, neuroinflammation, vascular amyloidosis, and widespread neuronal and synaptic degeneration (2). Mitochondria are dynamic organelles responsible for ATP generation and metabolic regulation, and are crucial for neuronal health and survival (3). In AD, mitochondrial dysfunction manifests as impaired oxidative

phosphorylation, reduced ATP production, overproduction of reactive oxygen species (ROS), and disrupted calcium homeostasis, exacerbating synaptic failure and neuronal death (4,5). Mounting evidence highlights a "vicious cycle" in which mitochondrial disturbances promote A β deposition and tau phosphorylation (6). Additionally, mitochondrial dynamics (Fission and fusion) imbalance and reduced biogenesis further impair neuronal energy metabolism and resilience (7). Recent literature emphasizes that mitochondrial abnormalities, including oxidative stress and mitophagy dysfunction, are closely intertwined with AD pathology and accelerate neurodegeneration.

A key mechanism for maintaining mitochondrial integrity is mitochondrial proteostasis, which involves the mitochondrial unfolded protein response (UPR^{mt}) and mitophagy, the selective removal of damaged mitochondria (2,3). UPR^{mt} also activates SIRT3 and antioxidant enzymes as part of proteostasis responses. Mitophagy can occur basally, ensuring regular turnover under normal conditions, and can be induced in response to stress. Its regulation is governed by pathways including PINK1/PARKIN, AMPK, and SIRT1 (5). Basal mitophagy supports homeostasis, while induced mitophagy protects neurons from mitochondrial insults. However, the interplay among mitophagy, mitochondrial biogenesis, and dynamics remains poorly understood in AD models, constituting a major gap in knowledge (8).

Non-pharmacological interventions such as aerobic exercise and resveratrol (RSV) have gained attention for modulating mitochondrial function (9,10). Exercise activates AMPK/NAD⁺-dependent signaling, promotes mitochondrial biogenesis via PGC-1 α , and improves dynamics (11,12). Studies in Parkinson's disease models demonstrate that treadmill running improves mitochondrial dysfunction by increasing mitophagy markers such as PINK1, PARKIN, and p62 (13). RSV, a polyphenol, exhibits antioxidant and anti-inflammatory properties, enhances biogenesis via AMPK/PGC-1 α , and activates mitophagy through the PINK1-PARKIN and SIRT1 pathways (14). However, clinical translation is limited by RSV's poor bioavailability,

rapid metabolism, and limited blood-brain barrier penetration; novel delivery approaches are being explored (15). Clinical findings remain inconsistent due to variability in dosage, duration, study design, and population heterogeneity (9). Some trials report cognitive benefits and reduced Aβ pathology, while others show minimal effects, highlighting ongoing controversies. An animal study combining aerobic training and RSV demonstrated synergistic activation of the AMPK/PGC-1α/SIRT1 pathway in AD models, with combined treatment outperforming individual interventions (16). Despite this evidence, no prior studies have comprehensively examined the combined effects of exercise and RSV on multiple mitochondrial quality-control mechanisms - mitophagy, biogenesis, and dynamics - in AD models. Addressing this gap holds significant clinical relevance, as targeting several aspects of mitochondrial health may better preserve cognition and delay AD progression (17).

Therefore, this study aimed to explore the synergistic effects of aerobic exercise and RSV on mitophagy in the hippocampal tissue of AD rats. We hypothesized that combined treatment would synergistically enhance mitophagy, mitochondrial biogenesis, and dynamics via the SIRT1/PINK1/PARKIN signaling pathway, ultimately improving mitochondrial function and cognitive performance.

Methods

This laboratory-based experimental study was conducted in accordance with animal protection policies outlined by the Helsinki Convention and the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals. The experimental protocol was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Islamic Azad University, Ayatollah Amoli Branch (Approval code: IR.IAU.MAMOL.REC.1403.174).

Thirty-five 8-week-old male Wistar rats (Average weight 223.17 ± 9.08 g) were selected, as this age corresponds to young adulthood in rats and is suitable for modeling early-stage Alzheimer’s disease. Male rats were chosen to avoid hormonal fluctuations associated with the estrous cycle that could affect experimental outcomes. All rats underwent veterinary screening to confirm good health and the absence of pre-existing conditions. Rats were housed under controlled conditions (22 ± 3°C, 12:12-hour light-dark cycle) with ad libitum access to water and a standardized rodent diet (20% protein, 5% fat, 55% carbohydrate, and essential vitamins and minerals). The sample size of seven rats per group was determined based on prior studies and calculated to achieve a statistical power of 80% with an alpha level of 0.05 to detect significant differences in mitochondrial autophagy markers.

After a one-week acclimatization period-including daily handling and habituation to the treadmill apparatus to reduce stress and improve exercise compliance-the rats were randomly assigned into five groups of seven rats each: (1) Normal (NO), (2) Alzheimer’s (AD), (3) Alzheimer’s-Training (ADT), (4) Alzheimer’s-Resveratrol (ADRSV), and (5) Alzheimer’s-Training-Resveratrol (ADTRSV). Randomization was performed using a computer-generated random number sequence.

Alzheimer’s induction

Amyloid-β 1-42 (Sigma-Aldrich) was dissolved in double-distilled sterilized water and incubated at 37°C for one week to promote aggregation. The solution was stored at 4°C and used within 24 hours to maintain peptide integrity. Rats were anesthetized with ketamine (50 mg/kg) and xylazine (5 mg/kg), and placed in a stereotaxic apparatus. The scalp was shaved, and bregma and lambda sutures were identified via sagittal incision. Stereotaxic coordinates for the CA1 hippocampal region were AP -3.6 mm, ML ±2.0 mm, DV -2.8 mm from bregma. Using a Hamilton syringe, 2 μL of amyloid-β solution was injected into the hippocampus over one minute. The needle was left in place for five minutes to prevent backflow before withdrawal (18).

Exercise protocol

The exercise regimen, as shown in Figure 1, commenced at two months of age and included two stages: familiarization (2 weeks) and adaptation to the full training protocol (8 weeks). During familiarization, rats performed treadmill exercises at 6-18 meters per minute for 15-45 minutes, five sessions in the first week, corresponding to moderate-intensity exercise. This speed corresponds to moderate-intensity exercise for Wistar rats, approximately 60-70% of their maximal oxygen uptake (VO₂max), and is effective in inducing mitochondrial adaptations without causing excessive fatigue (19). The subsequent 8-week period involved running at 18 meters per minute for 45 minutes, five days per week (20).

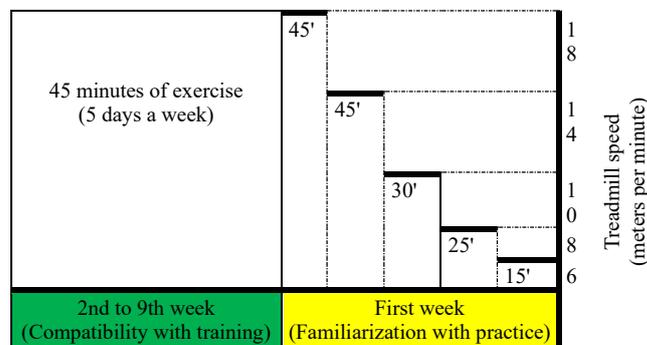


Figure 1. Exercise protocol

Resveratrol administration

Resveratrol (20 mg/kg, Sigma-Aldrich) or an equivalent volume of saline was administered orally by gavage every morning (8:00-10:00 AM) for eight weeks (21).

Tissue collection and assay validation

Forty-eight hours after the last training session, and following 12-14 hours of fasting, the animals were anesthetized and sacrificed. Hippocampal tissue was isolated, washed in saline, placed into tubes containing RNA preservative, rapidly frozen in liquid nitrogen, and stored at -80°C until analysis. Table 1 presents the primer sequences used for PINK1, PARKIN, and GAPDH. Total RNA was extracted, reverse-transcribed into complementary DNA (cDNA), and analyzed by PCR to assess gene expression.

Real-time PCR

Twenty milligrams of tissue were minced and total cellular RNA was extracted using thiazole solution. cDNA synthesis was performed via reverse transcription. The cDNA was amplified using SYBR Green master mix (Thermo Scientific, USA) and the primers listed in Table 1. For mRNA quantification, 1 μg of total RNA was treated with RQ1 RNase-free DNase I enzyme (Promega) prior to reverse transcription. The thermal cycling protocol consisted of an initial denaturation at 95°C for 10 minutes, followed by 40 cycles of 20 seconds at 95°C, 30 seconds at 60°C, and 50 seconds at 72°C. Gene expression was evaluated using the comparative threshold cycle (Ct) method, normalized as (Control Ct) - (Target Ct) = ΔCt, and relative gene expression was calculated using 2-ΔCt.

Statistical analysis

Data distribution was assessed for normality using the Shapiro-Wilk test and for homogeneity of variances using Levene's test. Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey’s post-hoc test. Data were analyzed with SPSS version 26, and statistical significance was set at P ≤ 0.05.

Table 1. Primer pattern of PINK1 and PARKIN

Genes	Forward primers	Reverse primers
PINK1	5'-TCTCCGCTGCTTCTCCTC-3'	5'-GGA CCGCTACCGCTTC TTC-3'
PARKIN	5'-ACGCTCAACTTGGCTACTC-3'	5'-CACTCCTCGGCA CCATAC-3'
GAPDH	5'-AGAAGGCTGGAGAAGATGAGG-3'	5'-TTGGTGCTCGTGTCTTCTGT-3'

Results

The average weight of the groups at baseline and after eight weeks is shown in Table 2.

At baseline, one-way ANOVA revealed no significant differences in body weight among the groups (P-Value = 0.783). Paired t-tests showed that after eight weeks, body weight increased significantly compared with baseline in the NO, AD, ADT, ADRSV, and ADTRSV groups (All P-Value = 0.001). Between-group comparisons using one-way ANOVA demonstrated that the ADTRSV group had a slightly but statistically significantly higher body weight than the NO group (P-Value = 0.043).

Data analysis using one-way ANOVA revealed significant differences in PINK1 expression among groups (F = 13.031, P-Value < 0.0001; Figure 2). Tukey's post-hoc tests demonstrated a significant decrease in PINK1 expression in the AD (P-Value < 0.0001), ADT (P-

Value = 0.024), and ADRSV (P-Value = 0.032) groups compared to the NO group. A significant increase was observed in the ADT (P-Value = 0.043), ADRSV (P-Value = 0.033), and ADTRSV (P-Value < 0.0001) groups compared to the AD group. ADTRSV showed higher PINK1 levels than both ADT (P-Value = 0.036) and ADRSV (P-Value = 0.046) groups.

Similarly, one-way ANOVA revealed significant differences in PARKIN expression among groups (F = 16.851, P-Value < 0.0001; Figure 3). Tukey's post-hoc tests indicated a significant reduction in PARKIN expression in the AD (P-Value < 0.0001), ADT (P-Value = 0.006), and ADRSV (P-Value = 0.001) groups compared to the NO group. Significant increases were observed in the ADT (P-Value = 0.005), ADRSV (P-Value = 0.046), and ADTRSV (P-Value < 0.0001) groups compared to the AD group, with ADTRSV exhibiting higher PARKIN levels than the ADRSV group (P-Value = 0.046).

Table 2. Comparison of average body weight among groups at baseline and after 8 weeks

Groups		NO (n=7)	AD (n=7)	ADT (n=7)	ADRSV (n=7)	ADTRSV (n=7)
Weight (Grams)	First week	219.71±10.61	225.57±11.28	224.71±9.41	222±6.42	223.86±8.49
	Eighth week	240.14±11.46*	239.14±11.21*	240.43±7.61*	236.71±8.46*	237.29±10.09 ^c

NO: Normal, AD: Alzheimer, ADT: Alzheimer-Training, ADRSV: Alzheimer-Resveratrol, ADTRSV: Alzheimer-Training-Resveratrol. * Difference from First week same group, c Difference from ADRSV group.

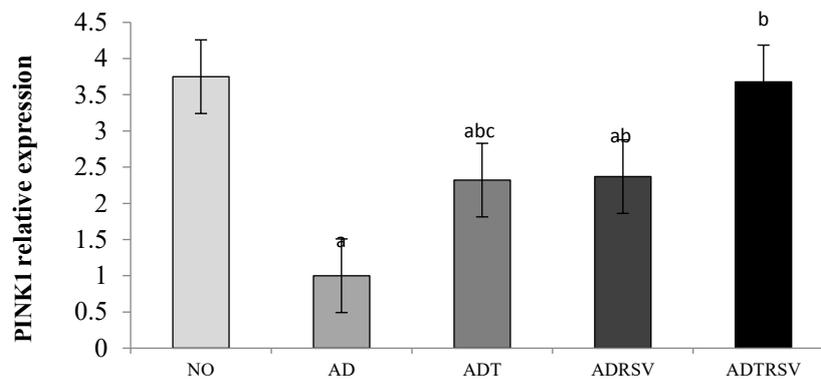


Figure 2. Expression levels of hippocampal PINK1 in different groups. a- Indicates significant decrease with the NO group; b- Indicates a significant increase with the AD group; c- Indicates a significant decrease with the ADTRSV group.

Abbreviations: NO: Normal group; AD: Alzheimer group; ADT: Alzheimer-Training group; ADRSV: Alzheimer-Resveratrol group; ADTRSV: Alzheimer-Training-Resveratrol group.

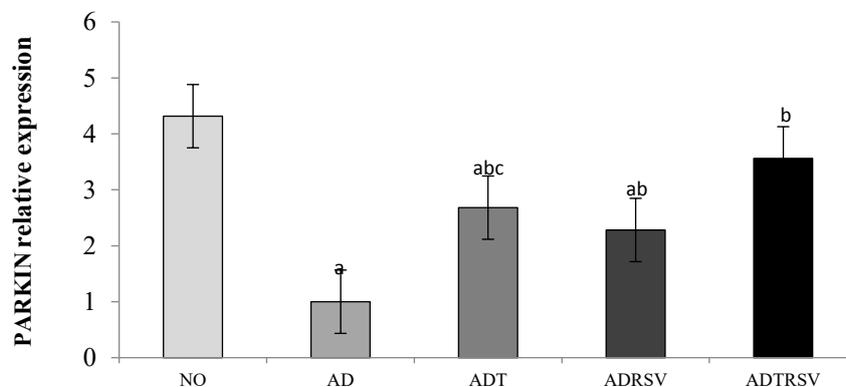


Figure 3. Expression levels of hippocampal PARKIN in different groups. a- Indicates significant decrease with the NO group; b- Indicates a significant increase with the AD group; c- Indicates a significant decrease with the ADTRSV group.

Abbreviations: NO: Normal group; AD: Alzheimer group; ADT: Alzheimer-Training group; ADRSV: Alzheimer-Resveratrol group; ADTRSV: Alzheimer-Training-Resveratrol group.

Discussion

This study demonstrated a significant reduction in PINK1 and PARKIN expression following Alzheimer's disease (AD) induction, reinforcing the critical role of the PINK1-PARKIN pathway in mitochondrial homeostasis and AD pathology. While previous studies, such as Fang et al. (2019), reported impaired mitophagy in AD models (22), our findings provide direct evidence linking decreased PINK1 and PARKIN expression to hippocampal mitochondrial dysfunction, a region crucial for memory and cognition. This supports the hypothesis that mitophagy impairment contributes to the accumulation of damaged mitochondria, exacerbating neuronal dysfunction and death in AD.

Clinical studies by Castellazzi et al. (2019) also suggest that autophagy-related proteins such as ATG5 and PARKIN could serve as early diagnostic biomarkers for cognitive decline in elderly AD patients (23). Our findings align with these observations and extend them by demonstrating that both aerobic exercise and resveratrol (RSV) supplementation can restore PINK1 and PARKIN levels, potentially counteracting mitophagy deficits in AD. While some studies have reported limited effects of resveratrol on cognition in clinical populations - likely due to bioavailability, dosage, and duration - our results confirm its potential to restore mitophagy in AD. Additionally, some studies have reported limited cognitive effects of RSV in clinical populations, highlighting the need to consider factors such as bioavailability, dosage, and treatment duration as potential confounders (24,25).

AD pathology is characterized by the accumulation of beta-amyloid plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein (26). Both A β and tau disrupt the PINK1-PARKIN pathway, increase ROS production, and damage mitochondrial membranes (27). Our findings corroborate this model by showing decreased PINK1 and PARKIN expression in AD rats, suggesting that impaired mitophagy is a key mechanism underlying mitochondrial abnormalities in AD. The PINK1-PARKIN pathway governs ubiquitin-dependent mitophagy, directing damaged mitochondria to lysosomal degradation and maintaining cellular homeostasis (28). Disruption of this pathway likely contributes to the accumulation of dysfunctional mitochondria, promoting oxidative stress and neuronal death. Alternative pathways, such as PGC-1 α -mediated biogenesis, AMPK/mTOR signaling, and NRF2-regulated antioxidant pathways, may also play important roles (29).

Exercise has emerged as a robust modulator of mitochondrial quality control. Previous reports confirm that aerobic exercise enhances PINK1-PARKIN-dependent mitophagy, improving resistance to mitochondrial decline and cognitive impairments in AD models (30-33). Mechanistically, exercise-induced mitophagy enhancement involves activation of signaling pathways such as the SIRT1-FOXO1/3 axis, which mediates PINK1/PARKIN expression in the hippocampus (34,35). Another pathway implicated is the Irisin/FNDC5-PINK1/PARKIN axis, where resistance exercise upregulates Irisin and FNDC5, leading to enhanced mitophagy and reduced oxidative stress (36,37). Our study did not directly measure these mediators, representing a limitation. Future research should incorporate assessments of SIRT1, AMPK, and related pathways to elucidate the molecular mechanisms underlying exercise-induced mitophagy improvements.

Resveratrol supplementation also significantly increased PINK1 and PARKIN expression in AD rats. Resveratrol is documented to induce autophagy via SIRT1 activation and AMPK phosphorylation (38,39), and it reduces unfolded protein response and inflammatory mediators, improves learning, and enhances proteostasis by modulating the AMPK/SIRT1 pathway (40-43). The antioxidant transcription factor NRF2, targeted by resveratrol, also regulates autophagy and proteasome proteins, which decline with age. Collectively, these mechanisms suggest resveratrol acts through multiple converging pathways to promote mitochondrial quality control.

Importantly, our study revealed that the combination of aerobic exercise and resveratrol supplementation produced a more pronounced increase in PINK1 and PARKIN expression than either treatment alone. This synergistic effect aligns with reports that exercise and resveratrol together enhance SIRT1 expression and reduce pro-apoptotic factors such as P53 (44). Combined treatment also reduces A β oligomers and modulates neuronal autophagy more effectively than single

interventions (45). These findings underscore the potential of multi-modal strategies targeting mitophagy to achieve greater therapeutic benefits in AD.

Despite these promising results, some conflicting evidence exists regarding the cognitive benefits of resveratrol in clinical trials, often attributed to bioavailability challenges, dosage variations, and differences in treatment duration (35,36). The precise molecular pathways by which exercise and resveratrol modulate mitophagy remain incompletely understood, with other signaling cascades such as AMPK/mTOR, PGC-1 α , and inflammatory pathways likely involved (46). Additional limitations include the absence of direct measurements of SIRT1 and AMPK activity and the lack of behavioral or cognitive outcome assessment. The relatively small sample size further limits generalizability. Future studies should address these gaps by including behavioral assessments, larger cohorts, and longitudinal designs to evaluate long-term effects of these interventions on mitophagy and cognitive function. Exploring dose-response relationships and optimizing treatment regimens will be essential for clinical translation. Investigating the interplay between mitophagy and other cellular processes, such as inflammation and proteostasis, may further clarify the complex pathophysiology of AD and identify new therapeutic targets.

Conclusion

In conclusion, this study demonstrated that Alzheimer's disease induction leads to a significant reduction in hippocampal PINK1 and PARKIN expression, indicating impaired mitophagy. Both aerobic exercise and resveratrol supplementation independently improved these indices, with their combination producing a synergistic effect. These results suggest that a multi-modal intervention combining exercise and resveratrol may effectively enhance mitophagy, maintain mitochondrial proteostasis, and contribute to the amelioration of AD pathology.

To build upon these findings, future research should:

- Directly measure key signaling mediators such as SIRT1 and AMPK to elucidate molecular mechanisms.
- Incorporate behavioral and cognitive assessments to link molecular changes with functional outcomes.
- Explore dose optimization, long-term effects, and translational potential in clinical or preclinical models.
- Investigate additional pathways influencing mitophagy and mitochondrial dynamics to develop comprehensive therapeutic strategies.

By addressing these areas, future studies can advance our understanding of mitophagy regulation in AD and facilitate the development of effective interventions to slow or prevent disease progression.

Acknowledgement

The authors gratefully acknowledge the Islamic Azad University, Sanandaj Branch, for administrative and laboratory support during this PhD dissertation project, which was conducted at personal expense.

Funding sources

This study was self-funded by the authors. No external funding or financial support was received from public, commercial, or not-for-profit agencies.

Ethical statement

All animal procedures were conducted in accordance with the guidelines of the National Institutes of Health (NIH) for the care and use of laboratory animals and were approved by the Research Ethics Committee of the Islamic Azad University, Ayatollah Amoli Branch (Approval code: IR.IAU.MAMOL.REC.1403.174).

Conflicts of interest

The authors declare that there are no conflicts of interest related to this study.

Author contributions

All authors contributed to the conception, design, execution, data analysis, and manuscript preparation. All authors read and approved the final version of the manuscript.

Data availability statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Cite this article as:

Heydarzadeh E, Azizbeigi K, Mohamadzadeh Salamat Kh. Aerobic exercise and resveratrol cooperatively modulate hippocampal mitochondrial mitophagy in Alzheimer's disease rat models. *Jorjani Biomedicine Journal.* 2025;13(3):25-30. <http://dx.doi.org/10.29252/jorjanibiomedj.13.3.25>