



The Effect of Aerobic Exercise and Resveratrol on OPA1 and DRP1 in Hippocampus Tissue of Rats with Alzheimer's disease

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ABSTRACT

Introduction: Mitochondrial abnormalities with impaired mitochondrial function play a role in the pathogenesis of Alzheimer's disease (AD). Mitochondrial metabolism in the brain is modulated by exercise activity and resveratrol (RSV). The aim of the present study was to determine the effect of aerobic exercise and resveratrol on hippocampal mitochondrial dynamics in rats with Alzheimer's disease.

Methods: In this experimental study, 35 eight-week-old male Wistar rats were divided into five groups: normal (NO), Alzheimer's (AD), Alzheimer's-training (ADT), Alzheimer's-resveratrol (ADRSV), and Alzheimer's-training-resveratrol (ADTRSV). The supplement groups received 20 mg RSV (per kg body weight) orally daily during the intervention period. The aerobic exercise program included treadmill running at a speed of 6-18 m/min, five days a week for eight weeks. For statistical analysis, differences between the NO and AD groups were assessed using an independent samples t-test. The effects of aerobic training, resveratrol supplementation, and their interaction were evaluated using two-way analysis of variance (two-way ANOVA), followed by the Bonferroni post hoc test. Effect sizes were reported as partial eta squared (η^2), and statistical significance was set at $p \leq 0.05$.

Results: AD induction caused a significant decrease in OPA1 expression and an increase in DRP1 expression compared with the NO group ($p=0.0001$). Aerobic exercise significantly increased OPA1 expression ($p=0.001$, $\eta^2=0.401$) and decreased DRP1 expression ($p=0.0001$, $\eta^2=0.546$). Resveratrol supplementation also significantly increased OPA1 expression ($p=0.001$, $\eta^2=0.379$) and decreased DRP1 expression ($p=0.0001$, $\eta^2=0.490$). No significant interaction was observed between exercise and resveratrol for either OPA1 ($p=0.962$, $\eta^2=0.000$) or DRP1 ($p=0.988$, $\eta^2=0.000$).

Conclusion: Mitochondrial dynamics are disrupted following induction of AD in hippocampal tissue, and exercise and resveratrol reduce the gap by increasing OPA1 levels and decreasing DRP. However, the combination of exercise and resveratrol did not have a synergistic effect on fission genes.

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Introduction

Alzheimer's disease (AD) is a chronic, progressive, and multifactorial neurodegenerative disorder associated with aging. It is characterized by progressive memory impairment, deterioration of cognitive and non-cognitive abilities, and alterations in personality and behavior (1). At the pathological level, AD is characterized by neuronal loss, neurofibrillary tangles, and amyloid- β (A β) plaque accumulation in brain regions such as the cortex and hippocampus (2). In addition to these classical hallmarks, increasing evidence indicates that disturbances in several essential cellular and molecular pathways substantially contribute to disease progression. Among these, mitochondrial dysfunction has emerged as a key pathogenic

mechanism. As the principal source of cellular energy, mitochondria generate adenosine triphosphate (ATP), which is indispensable for neuronal survival and normal physiological function (3). Previous studies have demonstrated markedly reduced ATP production in vulnerable brain regions of both AD patients and experimental animal models (4). Because neurons rely heavily on oxidative metabolism to satisfy their high energy demands, they are particularly susceptible to mitochondrial impairment. Dysfunctional mitochondria enhance the generation of reactive oxygen species (ROS), thereby promoting oxidative stress, neuroinflammation (5), and progressive neuronal injury during AD development (6). In addition, abnormalities in mitochondrial morphology, dysregulated

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mitochondrial gene expression, excessive free radical generation, increased lipid peroxidation, and impaired cytochrome c oxidase (COX) activity accompanied by reduced ATP synthesis have been consistently documented in AD. Collectively, these mitochondrial alterations play a central role in the onset and progression of the disease (7). Experimental evidence further indicates that A β accumulation is associated with reduced expression of the mitochondrial fusion protein OPA1 (8) together with increased expression of the fission protein DRP1 (9). Enhanced mitochondrial fission has likewise been observed in transgenic mouse models of AD (10). Growing evidence suggests that mitochondrial dysfunction represents one of the principal pathological mechanisms underlying age-related neurological disorders (11). Beyond defects in cellular bioenergetics and oxidative stress, recent findings indicate that impaired mitochondrial dynamics, mitochondrial biogenesis, and autophagy are closely associated with neurodegenerative processes during aging (12). Therefore, preservation of mitochondrial integrity and function appears to be essential for preventing mitochondrial dysfunction-related cellular damage and neuronal death (13). Accordingly, therapeutic strategies targeting mitochondrial dysfunction may provide an effective approach for slowing the progression of AD and reducing neurodegeneration.

Advancing age is the strongest risk factor for both the onset and progression of Alzheimer's disease, whereas physical inactivity has been identified as an important contributor to increased morbidity and mortality among affected individuals (14). Epidemiological evidence consistently demonstrates that regular physical activity is associated with a lower risk of AD and cognitive impairment, while randomized clinical trials have shown that aerobic exercise can delay disease progression and enhance cognitive performance (15,16). The neuroprotective effects of exercise are believed to involve multiple biological mechanisms, including enhanced neuroplasticity, improved cerebral perfusion, attenuation of inflammatory responses, and preservation of mitochondrial function (17). Indeed, prolonged aerobic exercise has been reported to improve learning and memory performance, attenuate oxidative stress, and activate beneficial signaling pathways within the hippocampus of experimental AD models (18).

Exercise is increasingly recognized as an effective non-pharmacological intervention for improving cognitive performance, restoring mitochondrial function, and delaying age-related

cognitive deterioration, particularly memory impairment (19). Furthermore, experimental evidence has shown that swimming exercise enhances cognitive performance, improves mitochondrial integrity, modulates mitochondrial dynamic proteins, and attenuates oxidative stress compared with sedentary animals (20).

Resveratrol has also attracted considerable attention because of its neuroprotective properties and its ability to improve cognitive function through potent antioxidant and anti-inflammatory activities (21). Its biological actions involve the regulation of multiple signaling pathways, including activation of sirtuin 1 (SIRT1), AMP-activated protein kinase (AMPK), and nuclear factor erythroid 2-related factor 2 (NRF2), all of which play essential roles in cellular stress adaptation, energy homeostasis, and antioxidant defense (22). In experimental models of AD, resveratrol has been shown to reduce biomarkers of neurodegeneration and inflammation in cerebrospinal fluid, suppress A β production and aggregation, and inhibit tau hyperphosphorylation (23). Moreover, enhancement of endogenous antioxidant enzyme activity together with attenuation of lipid peroxidation further contributes to its neuroprotective effects (23). Recent studies have also suggested that combining exercise with polyphenol supplementation may produce complementary or even synergistic neuroprotective benefits, highlighting their therapeutic potential for Alzheimer's disease (24).

Despite these promising findings, the molecular mechanisms through which resveratrol improves mitochondrial function in Alzheimer's disease remain incompletely understood. Although accumulating evidence supports the beneficial effects of both aerobic exercise and resveratrol in AD, the precise mitochondrial pathways responsible for these protective actions have not yet been fully elucidated. Therefore, the present study was designed to investigate the effects of aerobic exercise and resveratrol supplementation on mitochondrial dynamics in the hippocampal tissue of rats with Alzheimer's disease.

Materials and Methods

This investigation was designed as a laboratory-based experimental study with a developmental research approach. All experimental procedures involving animals were performed in compliance with institutional animal welfare regulations, the principles of the Helsinki Declaration, and the National Institutes of Health (NIH) guidelines for

the care and use of laboratory animals. The experimental protocol received ethical approval from the Research Ethics Committee of Islamic Azad University, Sari Branch (Approval No. IR.IAU.SARI.REC.1404.156). A total of 35 male Wistar rats (8 weeks old) with a mean body weight of 223.17 ± 9.08 g were obtained from the Pasteur Institute and housed in the animal research facility. Animals were maintained under controlled environmental conditions at $22 \pm 3^\circ\text{C}$ with a 12-h light/12-h dark cycle and had unrestricted access to standard laboratory chow and drinking water. Following a one-week acclimatization period, the animals were randomly assigned to five experimental groups: normal control (NO), Alzheimer's disease (AD), Alzheimer's disease plus aerobic training (ADT), Alzheimer's disease plus resveratrol (ADRSV), and Alzheimer's disease receiving both aerobic training and resveratrol (ADTRSV).

Alzheimer's disease was induced using amyloid- β 1-42 (A β 1-42) obtained from Sigma-Aldrich. The peptide was initially dissolved in sterile double-distilled water and incubated at 37°C for one week before administration. Animals were anesthetized with intraperitoneal injections of ketamine (50 mg/kg) and xylazine (5 mg/kg) and then secured in a stereotaxic apparatus. After shaving the scalp and exposing the skull through a midline sagittal incision, the bregma and lambda landmarks were identified to determine the stereotaxic coordinates. A small cranial opening was created above the CA1 region of the hippocampus, and 2 μL of A β solution was slowly delivered using a Hamilton microsyringe over approximately one minute (25). Cognitive performance was subsequently evaluated using the Y-maze behavioral test, in which spatial working memory was assessed by recording spontaneous alternation behavior during an 8-minute testing session.

The aerobic exercise protocol is summarized in Figure 1. Treadmill training commenced when the animals reached two months of age and consisted of two sequential phases: a two-week familiarization period followed by an eight-week training period. During familiarization, the rats exercised five days per week for 15–45 minutes per session at treadmill speeds ranging from 6 to 18 m/min. After adaptation, the animals completed the primary training program, which consisted of treadmill running at 18 m/min for 45 minutes per session, five sessions per week, over a period of eight weeks (26).

Resveratrol (20 mg/kg; Sigma-Aldrich) or an equal volume of saline solution was administered orally to the animals by gavage each morning between 08:00 and 10:00 a.m. throughout the 8-week intervention period (27). At the end of the experimental protocol, all animals were sacrificed under identical baseline conditions, including 48 hours after the final exercise session and following 12–14 hours of fasting, using chloroform anesthesia. After excision, hippocampal tissues were immediately rinsed with saline and placed in tubes containing RNAlater solution to preserve RNA integrity. The samples were subsequently frozen in liquid nitrogen and stored at -80°C until further analysis. To minimize potential effects of circadian variation, tissue collection was performed within a fixed time window, beginning at 08:00 a.m. and ending at 11:30 a.m. The primer sequences used in the present study are presented in Table 1. Initially, specific primers were designed for the target genes. Total RNA was then isolated from hippocampal tissue samples and reverse-transcribed into complementary DNA (cDNA). Subsequently, gene expression levels were determined by amplifying the synthesized cDNA using the polymerase chain reaction (PCR) technique.

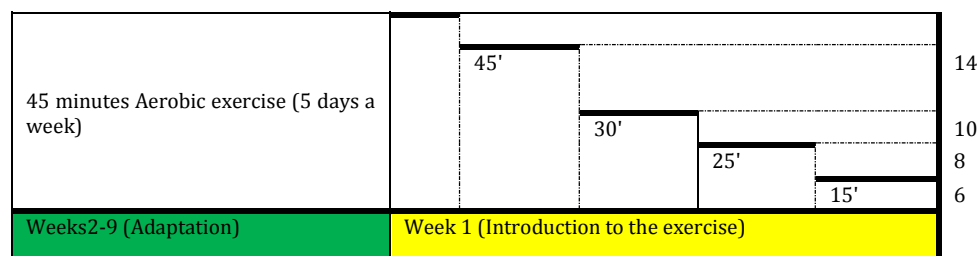


Figure 1. Exercise Protocol
* Treadmill Speed (m/min)

Table 1. Primer Pattern

Genes	Forward primers	Reverse primers
DRP1	5'-TGGATGTATTGATGGGAAGGGT-3'	5'-TTTCTGTTGGGCAGAGATGGGT-3'
OPA1	5'-GGATCTGCTGTTGGAGGTGG-3'	5'-GTCTTCTGAAGTGGGAAGGG-3'
GAPDH	5'-AGAAGGCTGGAGAAGATGAGG-3'	5'-TTGGTGCCTCCTGCTTCTGT-3'

Table 2. Results of independent t-test in the two NO and AD groups

Variable	p-value	t
DRP1	0.0001	10.414
OPA1	0.0001	8.813

Statistical Analysis

The data are expressed as mean $\pm$ standard deviation (Mean $\pm$ SD). The normality of data distribution was evaluated using the Shapiro-Wilk test. Differences between the NO and AD groups were assessed using an independent-samples t-test. The main effects of aerobic training (T), resveratrol supplementation (RSV), and their interaction (T $\times$ RSV) were examined by two-way analysis of variance (ANOVA), followed by the Bonferroni post hoc test for multiple pairwise comparisons. Effect sizes were calculated and reported as partial eta squared (η^2). All statistical analyses were carried out using SPSS software (version 26.0), with statistical significance established at $p \leq 0.05$.

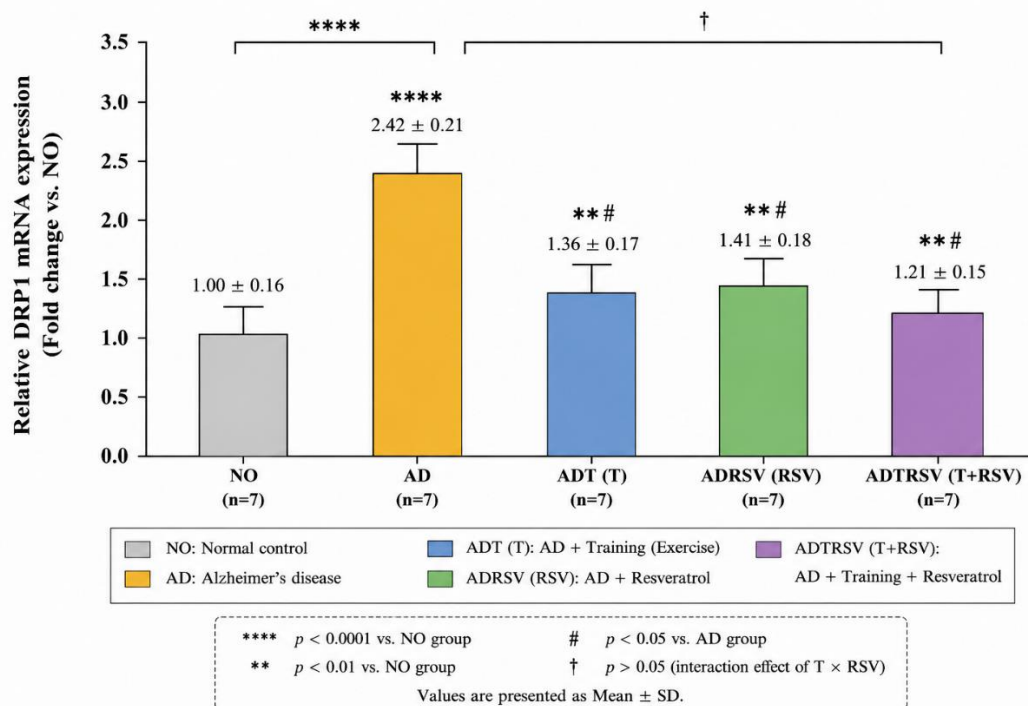
Results

The findings demonstrated that induction of Alzheimer's disease significantly altered the expression of the mitochondrial dynamic markers. Specifically, DRP1 expression was

significantly elevated ($p = 0.0001$), whereas OPA1 expression was significantly reduced ($p = 0.0001$) in the AD group compared with the NO group (Table 2).

Both aerobic exercise ($p = 0.0001$, $\eta^2 = 0.546$) and resveratrol supplementation ($p = 0.0001$, $\eta^2 = 0.490$) significantly downregulated DRP1 expression in the hippocampal tissue of AD rats. Nevertheless, the combined intervention did not produce a significant interaction effect on DRP1 expression ($p = 0.988$, $\eta^2 = 0.000$) (Figure 2; Tables 3 and 4).

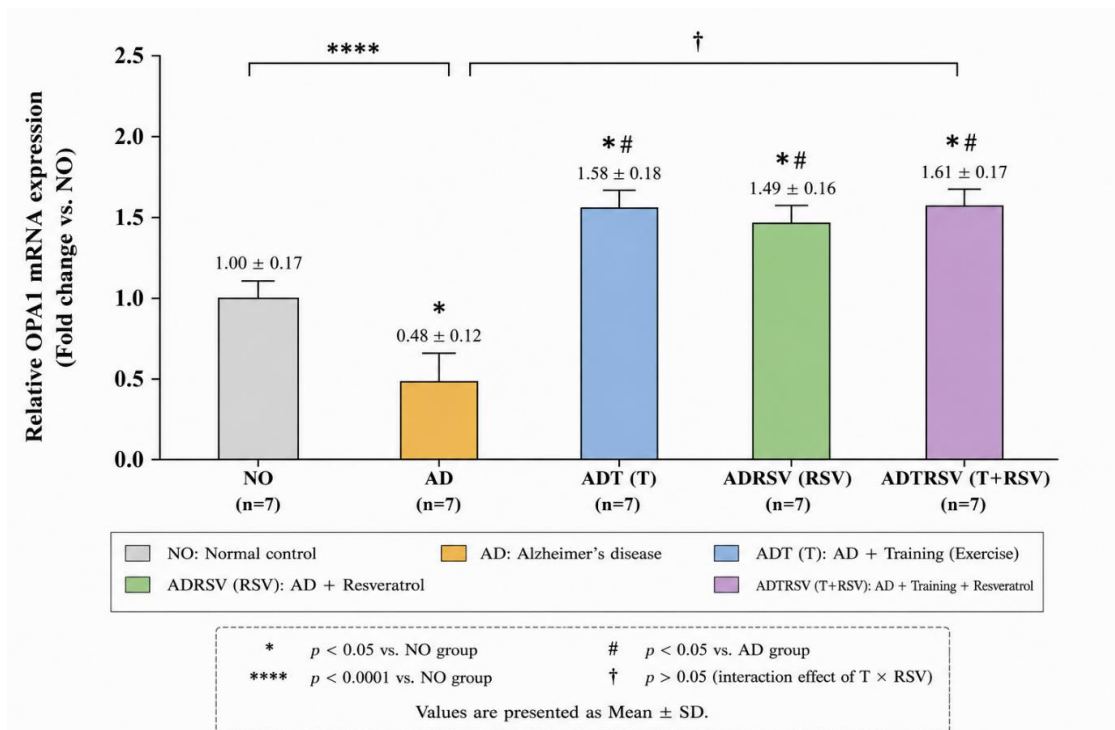
Analysis of OPA1 expression revealed significant main effects of both aerobic exercise ($p = 0.001$, $\eta^2 = 0.401$) and resveratrol supplementation ($p = 0.001$, $\eta^2 = 0.379$), both of which increased OPA1 expression in the hippocampal tissue of AD rats. In contrast, the combined intervention did not produce a significant interaction effect on OPA1 expression ($p = 0.962$, $\eta^2 = 0.000$) (Figure 3; Tables 5 and 6).

**Figure 2.** Effect of aerobic exercise and/or resveratrol supplementation on DRP1 mRNA expression in the hippocampus of AD rats.**Table 3.** Results of two-way analysis of variance for the effects of training (T) and resveratrol supplementation (RSV) on the expression of DRP1 levels

Source	Sum of squares	df	Mean squares	F	p-value	Eta squared (effect size)	power
T	37.839	1	37.839	28.833	.000	.546	.970
SUP	30.264	1	30.264	23.061	.000	.490	.999
T $\times$ SUP	.000	1	.000	.000	.988	.000	.996
Error	31.497	24	1.312				

Table 4. Bonferroni test results for pairwise comparisons of hippocampal tissue DRP1 expression for training (T) and resveratrol supplementation (RSV)

Groups 1	Groups 2	Average difference	Standard error	p-value
With T	No T	-0.318	2.235	0.0001
With SUP	No SUP	-0.279	2.079	0.0001

**Figure 3.** Effect of aerobic exercise and/or resveratrol supplementation on OPA1 mRNA expression in the hippocampus of AD rats.**Table 5.** Results of two-way analysis of variance for the effects of exercise (T) and resveratrol supplementation (RSV) on the expression of OPA1 levels

Source	Sum of squares	df	Mean squares	F	p-value	Eta squared (effect size)	power
T	.872	1	.872	16.043	.001	.401	.970
SUP	.796	1	.796	14.646	.001	.379	.956
T×SUP	.000	1	.000	.002	.962	.000	.050
Error	1.304	24	.054				

Table 6. Bonferroni test results for pairwise comparisons of hippocampal tissue OPA1 expression for training (T) and resveratrol supplementation (RSV)

Groups 1	Groups 2	Average difference	Standard error	p-value
With T	No T	-0.353	0.088	0.001
With SUP	No SUP	-0.337	0.088	0.001

Discussion

The present study demonstrated that induction of Alzheimer's disease was associated with a marked increase in mitochondrial fission-related gene expression together with a reduction in mitochondrial fusion-related gene expression. Specifically, AD induction significantly downregulated OPA1 while upregulating DRP1, indicating a profound disruption of mitochondrial dynamics. OPA1, an inner mitochondrial membrane GTPase, plays an essential role in mitochondrial fusion and is critical for preserving mitochondrial network

architecture, maintaining energy metabolism, and supporting neuronal survival (28). In contrast, DRP1 regulates mitochondrial fission by promoting the division of mitochondria into smaller organelles (29). Therefore, a shift toward excessive DRP1-mediated fission accompanied by reduced OPA1-dependent fusion results in mitochondrial fragmentation, which is considered one of the characteristic features of mitochondrial dysfunction during AD progression (30).

Recent studies published over the past few years have consistently supported these observations

and further emphasized the pivotal role of mitochondrial dynamics in Alzheimer's disease pathology. For instance, impaired mitochondrial morphology accompanied by reduced OPA1 expression has been reported in microglia from AD models, leading to diminished amyloid- β (A β) clearance capacity (28). Conversely, restoration of OPA1 expression enhances microglial A β clearance and alleviates cognitive deficits in experimental AD models (28). Likewise, an okadaic acid-induced cellular model of AD demonstrated significant downregulation of OPA1 together with increased phosphorylated DRP1 (pDRP1) levels, reflecting enhanced mitochondrial fission activity (31).

In addition, OPA1 has recently been proposed as a potential biomarker for Alzheimer's disease because of its close association with oxidative stress, impaired mitochondrial function, and hippocampal neurodegeneration (32). Collectively, these findings indicate that decreased OPA1 expression and elevated DRP1 levels are consistent pathological characteristics of AD and may represent attractive molecular targets for therapeutic intervention (33).

Given the essential role of mitochondrial dynamics in maintaining neuronal homeostasis, disturbances in the balance between mitochondrial fusion and fission may profoundly impair mitochondrial function, cellular bioenergetics, and redox regulation. Clinical and experimental evidence has demonstrated that altered mitochondrial dynamics in Alzheimer's disease are accompanied by excessive mitochondrial fragmentation, thereby contributing to disease progression (34). Excessive mitochondrial fission compromises ATP production by disrupting the assembly and efficiency of oxidative phosphorylation complexes, whereas reduced mitochondrial fusion limits mitochondrial repair by increasing the accumulation of dysfunctional organelles. Consequently, persistent disruption of the fusion-fission balance may ultimately impair synaptic function and accelerate neuronal degeneration (35).

The findings of the present study further demonstrated that aerobic exercise effectively restored mitochondrial dynamics in rats with Alzheimer's disease. Previous studies have indicated that aerobic exercise enhances mitochondrial quality and facilitates mitochondrial transport in experimental models of AD. This beneficial effect has been attributed, at least in part, to the transfer of healthy mitochondria from astrocytes to neurons, thereby improving neuronal bioenergetics and survival (36). Although OPA1 expression was not

directly evaluated in those investigations, improvements in mitochondrial quality are generally considered indicative of a healthier mitochondrial network, in which fusion-related proteins such as OPA1 play a fundamental role in preserving mitochondrial integrity and function (37). Consistent with these observations, dysregulation of mitochondrial fusion proteins, particularly OPA1, has been repeatedly documented in experimental models of Alzheimer's disease (37).

Previous evidence has also demonstrated that exercise attenuates mitochondrial dysfunction through modulation of signaling pathways associated with DRP1, thereby suppressing its activity and limiting excessive mitochondrial fission (38). These adaptations subsequently improve mitochondrial performance and cellular energy metabolism (38). Similar findings have been reported in experimental models of Parkinson's disease, where regular physical activity normalized mitochondrial fission, enhanced mitochondrial respiration, and reduced neuronal apoptosis through activation of the Irisin/AMPK/SIRT1 signaling pathway (39). Because excessive DRP1 activity has been implicated in the pathogenesis of numerous chronic disorders, particularly neurodegenerative diseases, reducing DRP1-mediated mitochondrial fission through exercise represents a promising therapeutic strategy (38). Moreover, abnormal mitochondrial dynamics, characterized by increased expression of mitochondrial fission proteins such as DRP1, are widely recognized as a hallmark of Alzheimer's disease pathology (40).

The findings of the present study are also in agreement with previous investigations. Ruegsegger et al. (2023) reported that high-intensity interval training (HIIT) improved mitochondrial dynamics in skeletal muscle by enhancing mitochondrial respiration, increasing the expression of the fusion protein OPA1, and reducing the fission protein FIS1 (41). Likewise, Lee et al. (2019) demonstrated that both high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) performed for 12 weeks significantly reduced hippocampal amyloid- β accumulation, attenuated mitochondrial fragmentation through reductions in DRP1 and FIS1, and improved mitochondrial morphology in APP/PS1 transgenic mice (42). Collectively, these findings support the concept that regular exercise restores the balance between mitochondrial fusion and fission, thereby contributing to the maintenance of neuronal integrity and brain function. In addition, exercise exerts pleiotropic biological

effects that preserve systemic homeostasis through modulation of mitochondrial function (43). Improvements in mitochondrial metabolism, biogenesis, and overall mitochondrial quality may explain the ability of exercise to delay mitochondrial dysfunction and disease progression (43). Nevertheless, not all studies have reported beneficial effects of exercise on mitochondrial fusion and fission markers (44). Such discrepancies may be attributable to differences in animal models, exercise modality, training intensity, intervention duration, and the methodologies used to assess mitochondrial dynamics.

Another important finding of the present study was that resveratrol supplementation significantly improved mitochondrial dynamics in rats with Alzheimer's disease. Previous investigations have demonstrated that resveratrol ameliorates neurological dysfunction primarily through enhancement of mitochondrial function (45). In addition, resveratrol has been shown to improve memory performance in experimental animals while increasing the activity of mitochondrial respiratory chain complexes II and IV within the hippocampus, suggesting that improved mitochondrial bioenergetics contribute to its cognitive benefits. Furthermore, resveratrol treatment increased DRP1 phosphorylation at Ser637, reduced total DRP1 protein expression, and simultaneously enhanced mitochondrial function (46). These findings are consistent with the results of the present study and further support the protective role of resveratrol in maintaining mitochondrial homeostasis under neurodegenerative conditions.

Several limitations should be acknowledged when interpreting the findings of this study. First, tissue samples could not be collected simultaneously from all animals, which may have introduced minor biological variability. Second, both the exercise protocol and resveratrol administration were imposed interventions, potentially generating physiological stress that might have influenced some experimental outcomes. Finally, because Alzheimer's disease is a chronic and progressive neurodegenerative disorder, the relatively short duration of the intervention may not have been sufficient to fully characterize the long-term effects of aerobic exercise and resveratrol on disease progression. Overall, the present findings suggest that both aerobic exercise and resveratrol supplementation improve mitochondrial dynamics by restoring the balance between mitochondrial fusion and fission. These adaptations may contribute to attenuation of

central nervous system damage associated with Alzheimer's disease. Although the present findings support the therapeutic potential of these interventions, the study was conducted in an experimental animal model. Therefore, translation of these results to clinical practice should be undertaken with caution, and additional well-designed human studies are required before recommending aerobic exercise combined with resveratrol supplementation as a therapeutic strategy for patients with Alzheimer's disease.

Conclusion

The present findings indicate that aerobic exercise and resveratrol supplementation independently improved mitochondrial dynamics in rats with Alzheimer's disease by increasing OPA1 expression and decreasing DRP1 expression. These adaptations suggest enhanced mitochondrial fusion together with reduced mitochondrial fission, which may contribute to the neuroprotective effects of both interventions. Nevertheless, no significant synergistic interaction was observed when aerobic exercise and resveratrol were combined. Future studies are needed to further elucidate the molecular pathways through which exercise and antioxidant supplementation modulate hippocampal mitochondrial dynamics and to determine their long-term therapeutic potential for Alzheimer's disease.

Declarations

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Conflicts of Interest

None of the authors of this article have any conflicts of interest with the publication of the article.

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Ethical Considerations

The present study has the ethical code of the Faculty of Medical Sciences, Islamic Azad University, Sari Branch, IR.IAU.SARI.REC.1404.156.

Authors' Contributions

All authors participated in the initial writing and revision of the article and, with the final approval of this article, accept responsibility for the accuracy and completeness of the content contained therein.

Artificial Intelligence (AI)

We have not used any AI tools or technologies to prepare this manuscript.

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