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Effects of Exercise Training and MitoQ on Cardiac Atrophy and Mitochondrial Dynamics in Aged Rats

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Abstract

Background: One global issue is population ageing and its associated consequences. This study aims to examine how endurance training and MitoQ supplementation can affect atrophy and mitochondrial dynamic signaling in the heart tissue of old rats.

Methods: In the present study, 28 male Wistar rats were divided into four groups, each with seven rats. The groups were: control, endurance training, MitoQ supplementation, and endurance training combined with MitoQ supplementation. In the training groups, the rats performed endurance training 5 days a week for 8 weeks. Also, MitoQ supplementation was administered in drinking water (250 μM) for 8 weeks. Western blotting and the real-time PCR method ($2^{-\Delta\Delta Ct}$) were used to measure the variables. The data were analyzed statistically using two-way ANOVA.

Results: The group that received ET+MitoQ had a much lower level of NF-κB gene expression than the control group, which was a significant difference ($P=0.04$). Also, this group had significantly lower MuRF gene expression than the control group ($P=0.002$). The ET group also showed significantly reduced MuRF gene expression compared to the control group ($P=0.04$). In addition, the ET group showed a significant decrease in FIS1 protein expression compared to the control group ($P=0.04$).

Conclusion: The combination of exercise training and MitoQ can have anti-inflammatory and subsequently anti-atrophic effects on cardiac tissue in aged rats. In addition, MitoQ supplementation alone may change mitochondrial dynamics in aged heart tissue. An increase in Drp1 expression (removing damaged mitochondria) and a reduction in Mfn1 expression (reducing oxidative stress) can have a protective effect on the aged cardiac muscle.

Keywords: Endurance training, Myocardium, Mitochondrial dynamics, Atrophy

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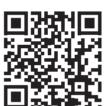
Introduction

Ageing is a real challenge for all countries, especially developing countries. Ageing increases the prevalence of diseases, which in turn has significant economic consequences and health costs. Cardiovascular disease, which increases with age, is among these diseases (1). As people get older, changes in heart tissue make it more likely that heart problems will develop and reduce the heart's ability to function correctly. These changes are mainly due to the buildup of collagen in the extracellular matrix, which both increases fibrosis and speeds up heart tissue (2).

One of the molecular pathways involved in atrophy is the ubiquitin-proteasome system, a primary regulator of protein degradation that provides a specific mechanism for the selective degradation of structural and regulatory proteins. This degradation system includes key enzymes, two inducible E3 ubiquitin ligases, atrogin-1 and MuRF1, which are significant factors in the degradation of skeletal and cardiac muscle in various atrophic conditions. The removal of these two factors from the cell can reduce muscle atrophy in response to nerve transection and lower limb suspension (3, 4). MuRF1 has been found in heart mitochondria and may help regulate mitochondrial function and reduce the production of harmful free radicals (5). In addition, studies have shown that activating NF-κB can induce the expression of proteins of the ubiquitin-proteasome system, leading to protein degradation (6). NF-κB controls the activity of genes involved in inflammation (7). NF-κB is linked to more than just cancer; it is also linked to the ageing process (8). As people age, this can throw off their body's balance and make them more likely to die from illnesses such as cancer, diabetes, or heart disease (9, 10). Also, when NF-κB remains active for a long time, it causes ongoing inflammation in heart tissue, leading to cell death and scarring of heart muscle cells. Studies have found that reactive oxygen species can activate toll-like receptor 4 (TLR4), which then reactivates NF-κB, forming a cycle that worsens inflammation and scarring in the tissue (11). However, NF-κB seems to be the main factor that connects all these pathways, because



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signals that make you age also turn on NF-κB, while signals that help you live longer stop its activation (12). NF-κB is a type of protein that responds to changes in the balance of chemicals inside cells, especially when there is an increase in harmful substances called reactive oxygen species. This protein helps cells deal with damage caused by these harmful substances (13). As people get older, oxidative stress builds up because the production of harmful reactive oxygen species increases, mitochondrial function declines, and the electron transport chain is disrupted. Other age-related factors also contribute to increased oxidative stress (13, 14).

Mitochondria are active parts of the cell that change shape, number, and where they are located inside the cell by fission and fusion. Under physiological conditions, the processes of fission and fusion remain balanced (15, 16). However, in some diseases, mitochondrial fission increases, which worsens as the disease progresses; for example, in diabetes, mitochondrial fission is higher in endothelial cells, and in pulmonary arterial hypertension, it is higher in pulmonary vascular smooth muscle cells. This increased fission impairs blood vessel function in both diabetes and pulmonary arterial hypertension (17, 18). Mitochondria help regulate ROS production, energy use, signals for cell death, and calcium balance in heart muscle cells. Mitochondria can be damaged, but processes such as fission and fusion are important for maintaining their proper function. These processes are managed by proteins called dynamin-related GTPases (19, 20). Proteins in the outer mitochondrial membrane, such as Mitofusin 1 and 2 (Mfn1/2), and proteins in the inner mitochondrial membrane, like optic atrophy 1 (Opa1), mediate mitochondrial fusion. At the same time, dynamin-related protein 1 (Drp1) links to its receptor proteins. The outer mitochondrial membrane also contains proteins such as mitochondrial fission protein 1 (MTFP1), MFF, and Drp1, which are involved in mitochondrial fission (21). MitoQ is an antioxidant that targets mitochondria. It contains a moiety called triphenylphosphonium (TPP +) and coenzyme Q10, which help it enter the cell mitochondria. MitoQ has been shown to help protect against various diseases, including some neurological conditions and diabetic kidney disease (22), due to its strong ability to neutralize harmful free radicals (23). A 2021 study by Jeong and others found reduced oxidative stress after 8 weeks of endurance exercise and MitoQ supplementation. This was evidenced by lower levels of markers such as 4-HNE and MDA. At the same time, the body's ability to fight oxidation improved, as evidenced by higher levels of enzymes such as catalase and SOD-1 (24). So far, most research looking at how MitoQ affects oxidative issues connected to ageing has mainly been done using rodent models (25), with a small number of human studies focusing mainly on patients with chronic diseases such as vascular dysfunction (26), hepatitis C (26, 27), or Parkinson's disease (28). Some studies in humans suggest that MitoQ alters mitochondrial function in tissues and reduces the production of harmful chemicals called ROS (29). However, this has not yet been carefully studied in humans. Middle-aged adults are the group that takes the most antioxidant supplements (30), and this is when the risk of age-related diseases begins to rise. It is important to determine whether mitochondrial-targeted antioxidants, such as MitoQ, can alter mitochondrial function and affect ROS levels in this age group. Earlier research has shown that MitoQ can mitigate mtDNA damage in human muscles during exercise (31).

Physical activity has been strongly linked to better health and a better quality of life for older people. Studies show that older adults who stayed active throughout their lives tend to have better metabolic health than those who were less active (32). Based on this, the first goal of this study was to examine how 8 weeks of endurance exercise and the antioxidant MitoQ might affect the muscle loss process and mitochondrial fission and fusion in the heart tissue of older male rats. The second goal was to see how doing both—endurance training and taking MitoQ—might influence the different factors involved.

Methods

Animals

In this experiment, 28 older male Wistar rats were purchased from the Kerman Physiology Research Centre. The rats were kept at around 22 °C, with a temperature variation of 2 °C, and exposed to a 12-hour light/12-hour darkness cycle. After one week of acclimatization (33), the animals were split into four groups at random ($n = 7$): Control: animals did not receive any treatment; endurance training: animals performed endurance training for 8 weeks, MitoQ supplementation: animals received MitoQ (250 µM dissolved in drinking water), and endurance training + MitoQ supplementation: performed endurance training and received MitoQ supplements for 8 weeks. The present study was conducted under the ethics code IR-KHU.KRC.1000.250 issued by the Ethics Committee of the Institute of Movement Sciences.

Moderate-Intensity Training Protocol

The rats were given 2 weeks to get used to the treadmill, running at 15 meters per minute for 15 minutes each time. To determine their maximum oxygen uptake, V_{max} was measured. Initially, the rats underwent an incremental test to determine Vmax. The incremental test began at 10 m/min, and the speed was increased in 3 m/min increments until the rats could no longer continue. After the test, lactate levels were measured using a lactometer from Lactate Scout Company (model number 37, Germany). Any lactate level above 6 mmol/L was considered high intensity for all the rats. VO2max was then calculated (33). Endurance training was performed according to the

relationship between calculated maximal oxygen uptake and treadmill speed; the intensity was adjusted during the training program by changing treadmill speed. Exercise training began at 30% of maximum speed for 10 minutes and, with progressive overload, reached 70% of maximum speed for 35 minutes over 8 weeks. Neither the control group nor the MitoQ supplement group exercised during the study. In each session, both were put on the treadmill to induce stress (33).

MitoQ Supplementation

MitoQ supplement with a purity of over 99% was purchased from MitoQ in New Zealand (B18050, Auckland, New Zealand). The supplement was given to rats at a concentration of 250 μM, mixed into their drinking water, for 8 weeks as instructed by the manufacturer (34). To check how much MitoQ reached the heart tissue, the total amount in the tissue samples was measured using HPLC-MS. To ensure accurate measurements, an internal standard, MitoQ, was used. This MitoQ was obtained from the MRC Mitochondrial Biology Unit and the Department of Medicine at the University of Cambridge. In heart tissue, the control group had no detectable levels of MitoQ, whereas the MitoQ group had a concentration of 5.23 ± 0.51 pmol/100 mg of protein.

Tissue Extraction

Forty-eight hours after the final training session, samples of cardiac tissue were collected. To obtain the samples, the animals were first anaesthetized by injection with xylazine and ketamine. Then, the left ventricle was removed and quickly frozen in liquid nitrogen. After that, the frozen tissue was moved to a freezer maintained at -80 °C for further testing (34).

Western Blotting Technique

The heart tissue was homogenized in a cold solution while kept on ice. The resulting mixture was then centrifuged at 14000 rpm at 4 °C for 15 minutes. The Bradford method was used to determine the protein content of the liquid portion of the tissue samples. Three samples, each weighing 40 mg, were collected from each group. These samples were loaded onto a 10% SDS-PAGE gel and then electrophoresed. After the movement was complete, the proteins were transferred onto nitrocellulose paper using an electric current of 200 milliamperes for 1 hour. Next, the membrane was blocked to prevent nonspecific binding, then incubated with antibodies specific for Drp1 and Mfn1. The antibodies used were HY-P80644 for Drp1 and 13798-1-AP for Mfn1. Antibody binding was detected on a special film using an enhanced chemiluminescence system, along with chemicals used for developing and checking the image. The images were then converted to digital format, and the brightness of the protein bands was measured using J-Image software. Then, the nitrocellulose papers were placed in a stripping solution at 55 °C for 30 minutes, rinsed with TBS, and then re-covered with a blocking solution for beta-actin (34).

Real-time PCR

Total RNA was extracted using the RNA Mini-Preps Super Kit (Catalogue No.: EX6031-SinaPure) according to the manufacturer's instructions. First, 20 mg of heart tissue was taken for each of the seven samples in each group. The tissue was processed according to the steps outlined in the RNA extraction kit. To remove the proteins, the sample was centrifuged at 12,000 g for 10 minutes, and the supernatant was carefully removed. This liquid was then mixed with the kit buffer at a 1:0.5 ratio and agitated for 15 seconds. After centrifuging at 12,000 g for 15 minutes at 4 °C, the liquid was separated into two fractions: one containing mineral components and the other containing water. The RNA sample was combined with the wash buffer at a 1:0.5 ratio and then centrifuged again. The RNA-containing tube was washed with ethanol, then dissolved in 20 mL of distilled water. The RNA concentration was measured using a NanoDrop device, and a 260:280 ratio of 1.8-2 was considered indicative of high-quality RNA. To create cDNA, 1 μg of RNA was used with a random hexamer primer and MMLV reverse transcriptase. For the cDNA synthesis, 100 ng of total RNA and a Parstous cDNA synthesis kit (Catalogue No: A101161, Parstous) were used.

Real-time PCR was performed using Master Mixes supplied by Ampliqon (Denmark). The PCR reaction included sterile water, forward and reverse primers and 100 ng of cDNA. The primers used had been tested for efficiency (90%) and were used to measure gene expression levels. Real-time PCR was performed on a StepOne Plus instrument (ABI, USA). The thermal cycle steps were: Step 1: denaturation at 95 °C for 10 minutes; Step 2: 40 cycles at 95 °C for 20 seconds and 60 °C for 30 seconds; and, finally, a melting curve analysis was performed, starting at 60 °C and increasing by 0.3 °C per step. The primers were purchased from Metabion (Germany) and are listed in Table 1. Finally, the gene expression levels

Table 1. Primers

Genes	Forward primer	Reverse primer
MuRF	CTTCATCCCAGTGGAGGAGATCC	CCAGAAGCTGCTAAGGTAGTCG
Nf-κB	TGAAGCCAGAGAACGTGTTG	ATAATTTGGCGATCCACAGC
18S	GAGGTGAAATTCTTGGACCGG	CGAACCTCCGACTTTCGTTCT

were determined using the $2^{-\Delta\Delta Ct}$ method, with the 18S gene serving as the reference gene (35).

Statistical Analysis

The results are shown as mean and standard deviation. The data were analyzed using Prism software, version 8.4.2 (GraphPad Software, San Diego, LLC, USA). The Shapiro–Wilk test was used to assess whether the data were normally distributed. A two-way analysis of variance (ANOVA) with Tukey's post hoc test was performed to compare group averages. *p*-values below 0.05 were considered statistically significant.

Results:

Figure 1 shows NF-κB gene expression, an inflammatory factor. Two-way ANOVA showed no significant interaction between ET and MitoQ ($F[1, 24] = 0.06$, $P = 0.8$). There was a significant effect of ET ($F[1, 24] = 5.60$, $P = 0.02$), but no significant effect of MitoQ ($F[1, 24] = 2.60$, $P = 0.11$) on NF-κB gene expression. MitoQ did not lower NF-κB gene expression in the MitoQ group compared to the control group ($P = 0.76$) (Figure 1). The group that received both ET and MitoQ had a significant decrease in NF-κB gene expression compared to the control group ($P = 0.04$).

Figure 2 shows how the MuRF gene is expressed as a factor linked to muscle shrinking. Two-way ANOVA found that the combination of ET and MitoQ together did not have a significant effect ($F[1, 24] = 0.97$, $P = 0.33$). However, ET had a significant effect on MuRF gene expression ($F[1, 24] = 8.88$, $P = 0.006$), and MitoQ also had a significant effect ($F[1, 24] = 7.308$, $P = 0.0124$). When looking at the MitoQ group alone, there was no apparent decrease in MuRF gene expression compared to the control group ($P = 0.06$) (Figure 1). The group that received both ET and MitoQ showed a significant decrease in MuRF gene expression compared with the control group ($P = 0.002$). Additionally, the group that received only ET al showed a significant decrease in MuRF gene expression compared to the control group ($P = 0.04$).

Figure 3 shows levels of Drp1, a protein involved in mitochondrial dynamics. A two-way analysis of variance revealed a significant interaction between ET and MitoQ ($F[1, 8] = 7.51$, $P = 0.02$). Both ET ($F[1, 8] = 68.04$, $P = 0.0001$) and MitoQ ($F[1, 8] = 43.60$, $P = 0.0002$) had statistically significant effects on Drp1 protein expression. However, MitoQ alone did not result in a significant increase in Drp1 protein levels compared with the control group ($P = 0.06$; Figure 3). The group that received both ET and MitoQ had a significant reduction in Drp1 protein expression compared to the MitoQ group ($P = 0.002$). Additionally, the ET group alone also showed a significant decrease in Drp1 protein expression compared to the control group ($P = 0.04$).

Figure 4 shows the protein levels of Mfn1, which is a factor involved in mitochondrial dynamics. Two-way ANOVA showed a significant interplay between ET and MitoQ ($F[1, 8] = 21.92$, $P = 0.001$). Additionally, there was a significant effect of ET ($F[1, 8] = 37.16$, $P = 0.0003$) and a significant effect of MitoQ ($F[1, 8] = 21.53$, $P = 0.001$) on Mfn1 protein levels. The MitoQ group had higher Mfn1 protein levels than the control group, though the difference was not statistically significant ($P = 0.06$; Figure 4). The

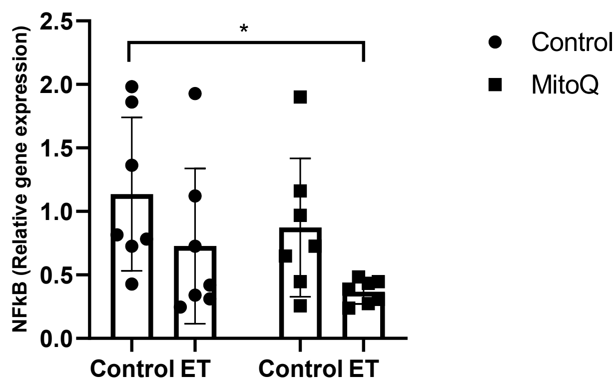


Figure 1. Impacts of ET and supplement on NF-κB in the heart tissue of aged rats. ET: endurance training; *: $P \leq 0.05$

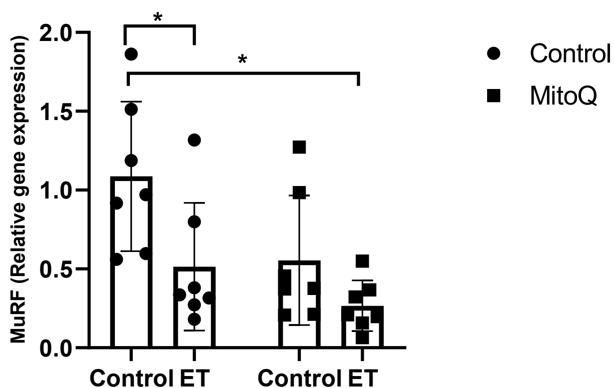
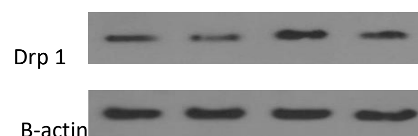


Figure 2. Impacts of ET and supplement on the MuRF in the heart tissue of aged rats. ET: endurance training; *: $P \leq 0.05$



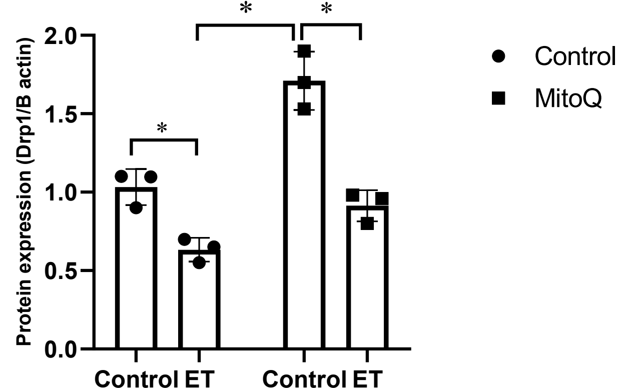


Figure 3. Impacts of ET and supplement on the DRP1 in the heart tissue of aged rats. ET: endurance training; *: $P \leq 0.05$

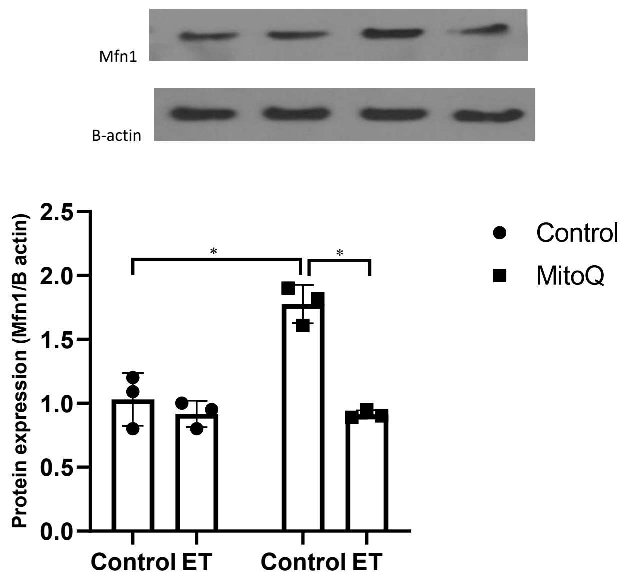


Figure 4. Impacts of ET and supplement on the Mfn1 in the heart tissue of aged rats. ET: endurance training; *: $P \le 0.05$

ET + MitoQ group had a significant decrease in Mfn1 protein levels compared to the MitoQ group ($P = 0.002$).

Discussion

In this study, using MitoQ alongside ET helped halt the process that causes muscle atrophy in older rats. In addition, this study shows that MitoQ can alter mitochondrial dynamics in cardiac tissue and stimulate fission and fusion processes in the heart. Meanwhile, the ET, in combination with MitoQ, may regulate mitochondrial dynamics.

It has been reported that the MuRF1 gene is upregulated in various forms of muscle atrophy in animal and human models (36), and it can be considered a valid marker of muscle atrophy. These genes encode E3 ubiquitin ligases, and although, under normal conditions, MuRF1- and atrogin-1-knockout rats appear phenotypically identical to their wild-type counterparts, these animals show little protection against muscle atrophy after denervation (37). In the present study, the hearts of aged rats expressed MuRF, which decreased following endurance training. Zanchi et al.'s results were consistent with those of the present study. They showed that after 3 months of resistance training, the expression of MuRF1 and Atrogin-1 decreased in the resistance training group (38). Another study found that problems with the body's redox balance contribute to muscle loss when muscles are not used for a long time; one mechanism is the activation of MuRF. Also, mitochondria in muscle cells are a major source of harmful substances called ROS, which are produced when muscles remain inactive for prolonged periods (39). Our results show that ET significantly decreased MuRF expression. We observed a reduction in the MitoQ group because of the antioxidant effect of this supplement, but the difference was not significant. Combining ET with MitoQ can increase MuRF expression in the heart muscle.

Several studies have shown that physical activity increases cardiovascular fitness throughout life and reduces age-related arterial stiffness and endothelial dysfunction in advanced age (40). Regular exercise reduces age-related oxidative stress, and 12 weeks of moderate-intensity treadmill aerobic exercise suppresses NF-κB activation in the aorta of aged rats and reduces IL-6 levels (41). Research on NF-κB activation in rat heart muscle after exercise is rare. Balan and others found that NF-κB activity in the heart increases two hours after exercise (42). Our results demonstrated that endurance training reduced NF-κB gene expression in heart tissue compared with the control group. However, when endurance training is combined with MitoQ, it has a much stronger effect in reducing NF-κB expression in the heart. NF-κB is involved in many important cellular processes, including inflammation, immune responses, the production of specific proteins, cell death, and cell growth and development (43). In line with our results, Aminizadeh et al. showed that MitoQ, as a beneficial immunoreactive agent, and exercise training have positive effects on NF-κB expression (34).

Exercise training is good for the heart, whether the body is healthy or dealing with illness. Research shows that being active helps lower the risk of heart problems and can improve heart function, especially after a period of reduced blood flow (44). Moderate-intensity endurance exercise improves the heart's ability to pump blood in older rats and promotes healthy heart growth (45). Mitochondria have recently been recognized as a novel target for the treatment of various diseases (46). In the heart, mitochondria perform important cellular functions, including breaking down molecules, building new ones, generating energy, regulating calcium levels, neutralizing harmful reactive oxygen species, and keeping cells alive. Mitochondrial dysfunction causes serious problems in heart disease by disrupting energy production, increasing harmful chemicals, and elevating intracellular calcium levels, which can lead to cell death (47). Fusion and fission help regulate mitochondrial quality by making new mitochondria and removing damaged ones. Studies show that during endurance exercise, skeletal muscle cells undergo increased mitochondrial fusion and fission (48). Mitochondria are active parts of cells that generate large amounts of reactive oxygen species, which are linked to the ageing process (49). Recently, there has been increased attention to antioxidants that target mitochondria to reduce ROS levels. MitoQ is a potent antioxidant that helps reduce oxidative stress in cells (50).

In the present study, ET reduced Drp1 protein expression in cardiac muscle, suggesting improved mitochondrial dynamics and reduced dysfunction. MitoQ showed a similar downward trend in Drp1 expression. Evidence indicates that, in ageing conditions, MitoQ can modulate mitochondrial dynamics, decreasing Drp1-mediated

fission and thereby attenuating mitochondrial dysfunction (51). The results of the present study contradict those of other studies conducted in young rats, which have shown some protective effects of MitoQ (52). Regular exercise reduces inflammatory markers, increases antioxidant capacity or activity, and reduces oxidative stress (53). When levels of oxidative stress markers decrease, this leads to higher expression of the MFn1 and MFn2 genes. This increased gene activity promotes mitochondrial fusion (54), and in our study, MitoQ, as an antioxidant, increased Mfn1 expression, which is associated with reduced oxidative stress in cardiac muscle. In the combination group, because oxidative stress is produced during ET (55), the protective effect of MitoQ may be reduced. Fusion and fission help maintain mitochondrial health by regulating mitochondrial quality. These processes include making new mitochondria and removing damaged ones through a process called mitophagy. Fission helps break damaged mitochondria apart so they can be removed and new mitochondria can take their place. A protein called Drp1, which is part of a bigger group of proteins that use energy to work, and other related proteins in the mitochondria, are important for fission. When mitochondria are split, the damaged segments can be removed through mitophagy. Mitophagy is a specialized form of cellular cleanup that prevents unhealthy mitochondria from clumping and helps prevent heart muscle cells from malfunctioning or dying. As people age, the benefits of heart-protecting treatments decrease due to several harmful changes within cells. Our findings show that MitoQ can help restore heart-protecting functions in older cells by promoting the splitting and merging processes in heart muscle cells. Hence, increasing the potency of therapeutic interventions in ageing conditions becomes essential (56). In a study using mice with severe hypertension, MitoQ improved heart contractility and maintained mitochondrial function (57). One of the project's limitations was the absence of groups with young rats; including young rats in the study could provide a clearer picture of how ageing changes over time. In addition, we did not examine different doses of the MitoQ supplement, which is another limitation of our study.

Conclusion

In sum, exercise training alone can have a protective effect on cardiac tissue in aged rats, but when combined with MitoQ, those effects can be further increased. MitoQ, as an antioxidant, may play a crucial role in mitochondrial dynamics, especially in aged cardiac tissue. Meanwhile, exercise training and MitoQ supplementation can have an anti-ageing effect on cardiac tissue.

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Authors' Contribution

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Validation: Elham FarhadFar.
Visualization: Elham FarhadFar.
Writing–original draft: Sadollah Salarmohammadi, Elham FarhadFar, Zahra Sarlak.

Competing Interests

The authors declare that they have no conflicts of interest.

Data Availability

All data is presented as part of the tables or figures. Additional data can be requested from the corresponding author.

Ethical Approval

The present project was conducted under the ethical code IR-KHU.KRC.1000.250, issued by the Ethics Committee of the Institute of Movement Sciences.

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